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MAJOR SURGERY IN THE AGED*

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AN abundance of statistical data testify to the fact that the population of the United States is in a phase of rapid expansion and of simultaneous aging. The application of these two facts to the problem of surgery in the aged is immediately apparent from consideration of the numbers by decades of persons in this country past the age of seventy in the years 1900 and 1950 and projected figures for the year 1960 (Table 1).

It is obvious that the problem of surgery in the aged has become one of major importance because of the sheer number of persons involved. The philosophy expressed in a phrase still frequently heard — "Why not let the poor old man die in peace?" — can hardly be regarded as acceptable when there are 8,000,000 to 9,000,000 people past the age of seventy, among whom the incidence of surgical disease is disproportionately high.

It is to be expected that the frailties imposed by advancing years will increase the hazards of surgery in the aged. Pediatric surgeons have repeatedly pointed out that the infant or small child cannot be regarded as a small-sized adult; so, too, the old patient cannot be regarded simply as a person who has enjoyed a longer span of life. This is not to suggest a need for geriatric surgeons, but the surgeon who accepts responsibility for the management of surgical problems in the aged must, if he wishes to maintain an acceptable mortality and morbidity rate, be thoroughly familiar with the special problems imposed by age and willing to expend the time and effort required to deal with them.

Viewed broadly, the special problems encountered in surgery of elderly people are the result not only of the aging process but also of the accompanying chronic medical diseases that are frequently present. Age is a vascular question,[2] depending in the first place on the quality of the vital rubber man inherits and, secondly, on the wear and tear to which it is subjected.

This deterioration of the vital rubber of the vascular system, which in varying degree is a characteristic finding in the aged person, has a profound effect on all his homeostatic mechanisms. Cardiac, pulmonary and renal reserves are diminished, vital capacity is lowered, and metabolism proceeds at a slower rate. The mechanisms that protect the standard-risk patient against the trauma and blood loss of surgery, against hypoxia and periods of hypotension and against change in external heat or cold are greatly impaired in the aged patient. Cannon[3] has expressed this as follows:

> . . . his homeostasis of acid base balance is also adversely affected by the changes in lungs, blood vessels and heart, and there is a gradual narrowing of the capacity to adapt the needs of the organism to the special requirements of muscular effort [or of surgery]. These mechanisms work satisfactorily in a routine quiet existence, but stress, even slight stress, encroaches sharply on his limitations.

Obviously, the surgeon dealing with these greatly handicapped patients cannot permit himself the same degree of latitude that he enjoys with more robust persons.

The keynote to the successful surgical management of patients in this age group lies in the exercise of foresight and in the anticipation and the systematic elimination of all hazards so far as possible. It is only by the most persistent and relentless attention to detail that the mortality in this group can be kept at an acceptable level. This must begin with the initial evaluation of the patient, and in this nothing is of greater importance than the assessment of the amount of physical work or activity of which he has recently been capable. The existence of chronic medical disease must be

TABLE 1. *Population of the United States by Age in 1900, 1950 and 1960 (in Thousands).**

Age yr.	1900	1950	1960
70–74	886	3412	4353
75–79	521	2178	3075
80–84	253	1100	1647
85 and over	122	576	762

*Adapted from Monroe.[1]

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discovered before operation, and appropriate measures for optimum control carried out during the preoperative period.

The basic principles of the clinical management of the aged patient differ in no way from those employed in the standard-risk patient. However, deficiencies are apt to be exaggerated. Major degrees of malnutrition with extensive weight loss and associated deficits of total blood volume and intracellular potassium are common. These are corrected by the usual methods, oral alimentation being employed when possible, with a high-calorie, high-protein diet, supplemented with vitamins and with multiple transfusions. When oral alimentation cannot be utilized, these deficiencies must be corrected by intravenous feeding of appropriate electrolytes, blood plasma, glucose and protein hydrolysates; in the severely depleted patient the caloric demands ordinarily require the use of fat emulsions. The point of particular importance in the aged patient is that these corrective measures must be carried out with precision and to optimum levels within the limits of the time permitted by the urgency of the required operation. Even minor deficits of blood volume or mild degrees of anemia are poorly tolerated by the aged patient. Failing[4] makes the following point:

> Apnea of two minutes will reduce the oxygen concentration of the blood 50 per cent. A patient with a normal 15 grams of hemoglobin may be able to get by, but the patient with less hemoglobin, one with but 11 grams, for instance, having this 50 per cent decrease in oxygen carrying ability for even a few moments may suffer damage.

As Carp[5] has pointed out, delay at the wrong time may be very costly. In emergency situations such as visceral obstruction and spreading infection, prolonged periods of preparation cannot be tolerated. Fluid and electrolyte balance can usually be restored in a matter of hours, and in such situations no further delay is warranted.

One of the most important factors that contribute to the reduction of the risk of surgery in the aged is expert anesthesia. The extreme vulnerability to hypoxia and hypotension requires that the anesthetic be given by an anesthesiologist with a wide knowledge of pulmonary and circulatory physiology and with the resources at his command to prevent these dangerous complications. There is increasing evidence that many deaths from cerebral and coronary thrombosis, pulmonary embolism and pulmonary edema, often regarded as acts of Providence, are the result of these complications.

The number of serious pulmonary complications caused by inhalation of regurgitated gastric secretions can only be guessed at, but is undoubtedly high. Cutler, Makel and Beecher[6] carried out studies on 300 patients under general anesthesia and found that 79, or 26.3 per cent, regurgitated gastric secretions and that 49, or 16.3 per cent, aspirated gastric contents. Seventy per cent of those who aspirated gastric secretions had an intratracheal tube in place. This seems to us a strong argument for the use of a tube with an inflatable cuff, despite the fact that there are certain disadvantages associated with its use. It also indicates the advisability of ensuring an empty stomach at the beginning of operation, by intubation, if necessary, even when the tube is not otherwise required.

The conduct of the operation must be carried out with painstaking care. Old tissues are friable and diminished in tensile strength, vessels are sclerotic, and the most careful and gentle handling is imperative. Precision and accuracy in the construction of anastomoses is vital, for the ordeals associated with malfunctioning stomas or from even minor degrees of leakage at lines of anastomosis are ill tolerated and may be fatal.

The early postoperative period is a critical one for the elderly patient. The feeble cough reflex and the tendency to accumulation of excessive tracheobronchial secretions predispose to the development of atelectasis and pneumonia and should be vigorously combated by hyperventilation, frequent turning of the patient from side to side and the use of tracheal suction. Massive atelectasis that does not respond immediately to conservative measures should be treated by bronchoscopy. Persistent accumulation of tracheobronchial secre-

TABLE 2. *Types of Major Surgical Procedures.*

OPERATION	TOTAL	DEATHS
Abdominal:		
Biliary	81	7
Bowel	206	29
Gastric	53	7
Hernia	36	3
Pelvic	14	0
Exploratory	28	3
Appendectomy	7	0
Sympathectomy	11	0
Miscellaneous	7	2
Totals	443	51
Thyroid:		
Bilateral subtotal thyroidectomy	16	2
Hemithyroidectomy	6	0
Excision of thyroid adenoma	3	0
Recurrent thyroid tumor	1	0
Totals	26	2
Vaginal:		
Hysterectomy	6	0
Plastic repair	10	0
Vulvectomy	5	0
Total	21	0
Amputations (thigh)	25	6
Regional radical dissection:		
Radical mastectomy	29	0
Neck dissection	17	2
Axillary dissection	2	0
Inguinal dissection	7	0
Jaw resection	2	0
Neck dissection with jaw resection	6	0
Neck dissection with jaw resection and hemiglossectomy	1	0
Hemiglossectomy	2	0
Radical skin excision	12	0
Excision of multiple fistulas-in-ano	1	0
Totals	79	2
Miscellaneous	27	1

tions, despite intermittent tracheal suction for more than a few hours demands tracheotomy, a procedure that we believe will often be life saving.

TABLE 3. *Gastric Operations.*

OPERATION	TOTAL	DEATHS	MORTALITY %
Total gastrectomy	2	2	100.00
Subtotal gastrectomy	34	4	8.50
Other gastric operation	17	1	5.88
Totals	53	7	
Average			11.32

Ambulation on the first postoperative day should be carried out in all but rare cases.

Inlying gastric and intestinal tubes should be removed at the earliest possible moment. When pro-

TABLE 4. *Further Breakdown of Types of Operations.*

OPERATION	TOTAL	DEATHS	MORTALITY %
Abdominal	443	51	11.51
Thyroid	26	2	7.69
Vaginal	21	0	0
Regional radical dissection	79	2	2.53
Amputations (thigh)	25	6	24.00
Miscellaneous	27	1	3.70
Totals	621	62	
Average			9.98

longed use is necessary, plastic tubes are much less irritating than rubber and are better tolerated by the patient.

Detailed discussion of the postoperative electrolyte and fluid requirements is beyond the scope of this paper, and in any case these will be variable. The use of sodium chloride should be avoided during the first forty-eight hours, and overhydration and overchlorination should be guarded against at all times. In the complicated case with abnormal fluid losses, the requirements should be calculated with the greatest precision, regulated by carefully kept intake and output charts and checked by frequent blood chemical studies. The need for potassium in the patient with abnormal fluid losses should not be overlooked.

Cole[7] has advocated the use of ACTH and cortisone to improve operability. We have had no experience with this. Whether the advantage gained will more than offset the undesirable effects of these hormones in the aged must await further trial.

We have considered routine use of elastic stockings throughout the postoperative period to be of value in the prevention of phlebothrombosis and pulmonary embolism.

RESULTS OF TREATMENT

Our experience with major surgery in the aged consists of 621 operative procedures on 500 patients over seventy years of age (Tables 2 and 3). The operative mortality for the entire group was 9.98 per cent (Table 4).

TABLE 5. *Operative Mortality in Abdominal Operations.*

OPERATION	TOTAL	DEATHS	OPERATIVE MORTALITY %
Elective:			
Biliary	72	7	9.72
Bowel	173	19	10.99
Gastric	46	7	15.22
Hernia	26	1	3.85
Pelvic	14	0	0
Exploratory	28	3	10.71
Appendectomy	1	0	0
Sympathectomy	11	0	0
Miscellaneous	4	1	25.00
Totals	375	38	
Average			10.13
Emergency:			
Biliary	9	0	0
Bowel	33	10	30.30
Gastric	7	0	0
Hernia	10	2	20.00
Pelvic	0	0	0
Exploratory	0	0	0
Appendectomy	6	0	0
Sympathectomy	0	0	0
Miscellaneous	3	1	33.33
Totals	68	13	
Average			19.12

Table 5 shows the results in 375 elective abdominal operations, with a mortality rate of 10.13 per cent, and in 68 emergency procedures, with a mortality rate of 19.2 per cent, confirming the experience of others that the elderly patient does not tolerate emergency surgery well. This is a strong argument for the elective correction of surgical conditions such as hernias and gallstones before emergency situations develop.

An interesting comparison of results may be made between patients operated on in Boston hospitals and those operated on in out-of-town hospitals (Table 6). In both elective and emergency operations there is a significant difference in the mor-

TABLE 6. *Comparative Hospital Mortality.*

TYPE OF HOSPITAL	TOTAL OPERATIONS	DEATHS	MORTALITY %	ELECTIVE SURGERY			EMERGENCY SURGERY		
				TOTAL	DEATHS	MORTALITY %	TOTAL	DEATHS	MORTALITY %
In town	386	27	6.99	333	19	5.71	53	8	15.09
Out of town	235	35	14.89	211	28	13.27	24	7	29.17

tality rate. For the entire series of 386 operations in Boston hospitals the mortality was 6.99 per cent, as compared with a rate of 14.89 per cent for 235 patients operated on in out-of-town hospitals. For 333 elective operations in Boston the rate was 5.71 per cent, as compared with a rate of 13.27 per cent in 211 patients operated on elsewhere, and poorer risks have been accepted for surgery and surgical procedures of increasingly greater magnitude have been done, such as total gastrectomy, removal of multiorgans for advanced cancer and pancreatoduodenectomy.

Comparison of results with those reported by other authors is difficult because of variations in the minimum age chosen, as well as in the composition of the material (inclusion of minor cases) and the percentage of emergencies (Table 8).

Table 9 summarizes the causes of death in the fatal cases. The mortality from pulmonary complications and from peritonitis is similar to the findings of other authors.

TABLE 7. *Operative Mortality According to Various Periods.*

PERIOD	TOTAL OPERATIONS	DEATHS	OPERATIVE MORTALITY	ELECTIVE OPERATIONS			EMERGENCY OPERATIONS		
				TOTAL	DEATHS	OPERATIVE MORTALITY	TOTAL	DEATHS	OPERATIVE MORTALITY
			%			%			%
1935-1939	50	7	14 0	43	5	11.6	7	2	28.6
1940-1944	163	13	8 0	146	11	7.5	17	2	11.8
1945-1949	248	30	12.1	212	21	9.9	36	9	25.0
1950-1952	160	12	7.5	143	10	7.0	17	2	11.8
Totals	621	62		544	47		77	15	
Averages			10.0			8.5			19 5

The increased mortality rate in out-of-town hospitals was almost exactly twice that in the Boston institutions. This difference, we believe, is the result of a combination of factors, the most important being the lack, especially in the earlier years in the out-of-town hospitals, of adequate laboratory facilities, the lack of fully trained anesthesiologists, the lack of a trained resident staff, greater preoperative periods of delay in the emergency cases and a later detection of complications as they arose.

Table 7 shows the results of treatment broken down into three five-year periods and a final period of three years. This shows a substantial fall in mortality from the first to the last period: 14.0 to 7.5 per cent for the entire series; 11.6 to 7.0 per cent in elective cases; and 28.6 to 11.8 per cent in emergency cases. This decline in mortality is considered to be of greater significance than the figures indicate since it has been attained despite the facts that increasingly older patients and poorer and for emergency operations the rates were 15.09 per cent in Boston and 29.17 per cent out of town.

TABLE 8. *Comparison of Mortality Rates for Major Surgery.*

AUTHOR	MINIMUM AGE	NO. OF OPERATIONS	MORTALITY
	yr.		%
Parsons & Parks[8]	60	100	17.0
Carp[9]	60	851	17.3
Bosch et al.[10]	60	500	9.6
Haug & Dale[11]	60	314	9.0
Cole[7]	60	1019	5.1
Clagett[12]	65	1201	9.0
Hay[13]	70	536	16.6
Present series:			
All cases	70	621	9 9
Operations in Boston hospitals	70	386	6.9

TABLE 9. *Causes of Death.*

CAUSE	NO. OF DEATHS
Cardiac (coronary-artery disease, 8 cases)	18
Cerebrovascular	1
Pulmonary embolism	7
Pulmonary	8
(Pneumonia, 6 cases)	
(Atelectasis, 1 case)	
(Respiratory failure, 1 case)	
Peritonitis	10
Postoperative hemorrhage	1
Shock	3
Miscellaneous	14
Total	62

SUMMARY

A review of 621 operative procedures on 500 patients over the age of seventy is presented. The over-all mortality rate was 9.98 per cent. Emergency operations carried a considerably higher mortality rate — 19.48 per cent. Comparison of the earliest operated group with the last demonstrated a significant fall in mortality from 14 to 9.98 per cent for both elective and emergency cases and from 11.63 to 6.99 per cent in elective surgery and from 28.57 to 11.76 per cent in emergency surgery.

The mortality rate of patients operated on in Boston hospitals was almost exactly half that in out-of-town hospitals.

Some of the important factors in the attainment of a low mortality rate in this age group are discussed.

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SYNDROME OF ANEMIA, DYSPHAGIA AND GLOSSITIS (PLUMMER-VINSON SYNDROME)*

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An iron-deficiency anemia associated with chronic dysphagia and glossitis in women between forty and fifty years of age is now known as sideropenic dysphagia. Historically, the entity has borne the name of the Plummer–Vinson syndrome,[1, 2] but the characteristics of the dysphagia and anemia had received attention in medical literature before Vinson's report in 1922.[3-8] Classically, the patient complains of choking or fear of choking and delayed swallowing of food localized at the cricoid area of the neck. The onset of the dysphagia may be sudden but is often insidious and periodic. Frequent associated complaints are weakness, fatigue, nervousness and "dyspeptic" symptoms. Fissures at the corners of the mouth, pallor and atrophic mucous membranes of the oropharynx and tongue are usually noted. Marked weight loss is not a prominent finding. Koilonychia, an inflamed tongue and neurologic disturbances are not usual. The anemia is usually moderate in degree. The syndrome can only be set apart from typical iron-deficiency anemia by the presence of the characteristic dysphagia.

The pathogenic interrelations of the anemia, dysphagia and glossitis have been the subject of controversy since the early descriptions of the disease. Case summaries reveal that the anemia may precede or follow the onset of dysphagia.[3, 9, 10] Thus, the anemia need not be the result of nutritional imbalance. By the same token, these observations do not support the thesis that the glossitis and mucous-membrane changes reflect nutritional depletion.

It was the concept of Plummer[1] and Vinson[2] that the dysphagia represented hysterical spasm.[11] Kelly[3] and Paterson[4] postulated derangement of the nerve plexuses of Auerbach and Meissner to account for the symptoms. Inflammatory diseases, including streptococcal[12] and syphilitic[13] infections, have been mentioned in etiologic discussions of the dysphagia. In view of the x-ray and esophagoscopic demonstrations of horizontal bands, longitudinal folds and obstructive webs in the introitus of the esophagus[3, 4, 7, 8, 14-17] these contentions seem untenable. Suzman[18] has described the mucous membranes of the esophagus as an atrophic, hyperkeratotic and often desquamated mucosa. Muscle fragmentation and small round-cell infiltration were present in the submucosa. The obstructing bands or webs can be demonstrated by x-ray technics utilizing thick barium and observing delayed swallowing in the narrowed esophagus at the postcricoid area. The mucous membranes are extremely friable and readily broken down with the passage of the endoscope. Esophageal carcinoma is a reputed sequel in the syndrome,[19, 20] but it should be pointed out that most of the carcinomas of the upper esophagus occur in women of this age group.

The anemia of sideropenic dysphagia is microcytic and hypochromic. Most often it is moderate in degree, but it may be profound. The red-cell volumetric indexes are typical of those of classic iron-deficiency anemias. The serum iron concentrations are low, and the bone-marrow sections are devoid of stainable iron stores; smears reveal a normoblastic hyperplasia. Achlorhydria is often seen but in the same frequency as that of pure iron-deficiency anemias. Splenomegaly occurs in the syndrome in ratios comparable with iron-deficiency anemia, and likewise koilonychia is observed in sideropenic dysphagia. The tongue is usually devoid of papillae, smooth and pale but rarely inflamed or sore. Fissures at the corner of the mouth are frequent and often accompanied by increased ptyalism.

Although recovery from this disease may be expected if iron is administered by mouth, in the 2 cases reported below different therapy was given

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in an attempt to separate the mucous-membrane changes from the manifestations of anemia.

Case Reports

Case 1. J. H., a 38-year-old English-born housewife, was seen in the Ear, Nose and Throat Clinic of the Henry Ford Hospital on April 22, 1952, complaining of dysphagia. Symptoms of weakness and fatigue beginning during pregnancy 4

Figure 1. *Marked Koilonychia before Iron Therapy in Case 1.*

years previously had led to the discovery of an anemia. The anemia was treated, but after the birth of the baby she had a uterine hemorrhage and a pulmonary infection. Within that year the weakness progressed, and the fingernails became brittle and concave. It was not until December, 1951, that she began to have difficulty in swallowing. All food seemed to lodge at the level of the cricoid cartilage.

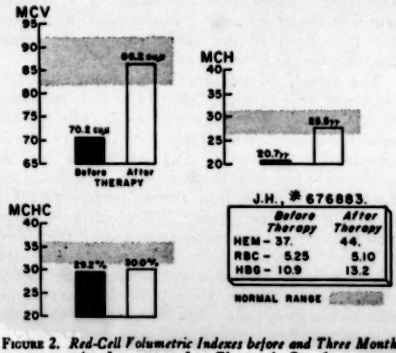

Figure 2. *Red-Cell Volumetric Indexes before and Three Months after Intravenous Iron Therapy in Case 1.*

On May 25 she was admitted to the hospital for study. The mucous membranes of the mouth were pale and atrophic, and no papillae were present on the tongue. Cheilitis was observed at the corners of the mouth. The fingernails revealed marked koilonychia (Fig. 1), but the physical examination was otherwise negative. She weighed 112 pounds, being within 3 pounds of her usual weight during the past 10 years.

Examination of the blood showed a red-cell count of 5,250,000, with a hemoglobin of 10.9 gm. per 100 cc. The cells were microcytic and hypochromic. The volumetric indexes of the red cells are shown in Figure 2. The hematocrit was 37 per cent; the platelets were 316,000, and the reticulocyte count 3 per cent. The serum iron concentration was 40 microgm. per 100 cc. Bone marrow on section revealed normoblastic hyperplasia and was devoid of stainable iron stores. Hydrochloric acid was present normally in the stomach. A barium swallow could not be interpreted as abnormal, but esophagoscopic examination demonstrated a friable stricture at the introitus of the esophagus.

Dilatation of the esophageal stricture had promoted normal swallowing by the end of the 2d postoperative day, and the patient began to take a normal diet within the 1st week. The anemia was treated rapidly by the intravenous injection of saccharinated iron. The patient received 5 daily injections of 100 mg. of iron, and she received 2 such injections in the 1st week after discharge from the hospital on June 2 and 2 injections at weekly intervals thereafter. By the 18th day after discharge the cheilitis had completely disappeared, and papillae were noted on the tongue. There was no dysphagia, and strength had returned. The fingernails had become less brittle and had begun to lose their concavity. The hemoglobin was 12.5 gm. per 100 cc. by this time, and iron was started by mouth. The progress of the red-cell indexes is noted in Figure 2. The serum iron at this time was 90 microgm. per 100 cc. Follow-up study in January, 1953, revealed absence of glossitis, anemia and koilonychia (Fig. 3); the patient felt well in all respects.

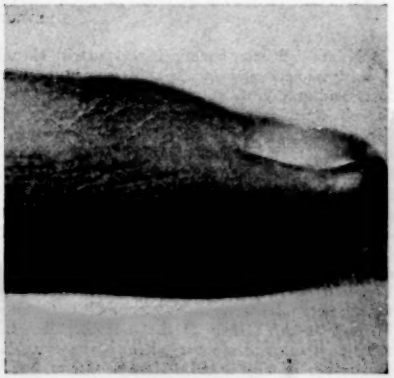

Figure 3. *Improvement in Koilonychia Six Months after Iron Therapy in Case 1.*

Case 2. L. S., a 48-year-old Scottish-born housewife, was admitted to the hospital on May 13, 1952, complaining of difficulty in swallowing and weakness. There was prominent pallor and marked debility. Cheilitis was present and the mucous membranes of the mouth were thin and glistening. The tongue was pale and devoid of papillae (Fig. 4). A tracheotomy scar was present, but the physical examination was otherwise negative.

The past history revealed that in 1934, during her 3d and last pregnancy, the patient had anemia. Achlorhydria was found, and a blood smear interpreted in a university hospital

confirmed a diagnosis of pernicious anemia, for which she was appropriately treated. Shortly after delivery difficulty in swallowing, localized to the cricoid area of the neck, developed. For years she had severe retching spells when food would lodge in her throat. During one of the attacks she suddenly had pain in the throat, and swelling of the neck, stridor and cyanosis rapidly developed. She was admitted to the hospital in December, 1944, with acute rupture of the esophagus and was treated with antibiotics and tracheotomy. After recovery from this

FIGURE 4. *Glossitis and Cheilitis on Admission in Case 2.*

severe illness she was followed in the Outpatient Department for fatigue, anemia and dysphagia, and despite energetic treatment a microcytic hypochromic anemia failed to respond. Her weight had averaged 110 pounds during this period of observation.

During this admission the hemoglobin was 9.5 gm. per 100 cc., and the red-cell count 5,080,000. The hematocrit was 36.6 per

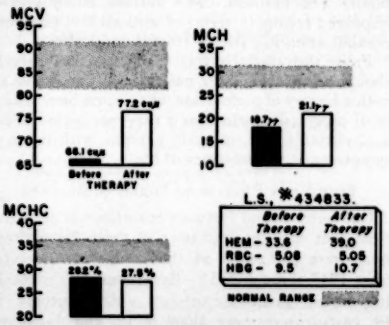

FIGURE 5. *Red-Cell Volumetric Indexes before and One Month after Alimentation Therapy in Case 2.*

cent, and the red cells were microcytic and hypochromic. The red-cell volumetric indexes are shown in Figure 5. Bone-marrow section revealed normoblastic hyperplasia, but there were no stainable iron stores. A Levin tube could not be passed to complete a gastric analysis. X-ray studies of the esophagus disclosed narrowing of the introitus and a small diverticulum in this area. Serial esophagoscopies in the previous several years were compatible with the syndrome of sideropenic dysphagia.

In the treatment of this patient hyperalimentation studies were made, without supplemental iron or vitamin therapy. An alimentation method was utilized,* the patient being fed through a polythene tube passed into the stomach. The feedings were given 3 times daily, averaging about 4000 calories for 2 weeks. Before discharge on June 2 the cheilitis had disappeared, and definite papillae were noted on the tongue. She volunteered the information that she had gained in strength, and a weight gain of 9 pounds was observed during this period. After going home she used the tube feeding for her evening meal for 2 weeks. At the end of this time the mucous membranes of the mouth had completely regenerated (Fig. 6), and the dysphagia had decreased in severity. One month after discharge it was necessary to add

FIGURE 6. *Improvement in Glossitis and Cheilitis after One Month of Alimentation Therapy in Case 2.*

iron by mouth to the program to aid in alleviating the anemia. Progress studies of the anemia are to be noted in Figure 5.

DISCUSSION

Case 1 indicates the rapid correction of the hypochromic anemia and the mucous-membrane changes with the intravenous use of iron while the patient is on a full diet. Case 2 illustrates the rapid regeneration of the mucous membranes by means of hyperalimentation technics without supplemental iron or vitamins. Again, it should be emphasized that these patients will recover on iron by mouth and that neither tube feeding nor intravenous administration of iron is essential therapy. This paper is not intended for a discussion of the value of a liquefied normal diet but is a confirmation of the rationale of its use. Furthermore, the occurrence of rupture of the esophagus in the syndrome of sideropenic dysphagia (Case 2) is considered to be of interest.

SUMMARY

A review of the syndrome of anemia, dysphagia and glossitis is presented.

Intravenously administered iron rapidly corrects the iron-deficiency anemia of sideropenic

* Dr. James Barron, of the Department of Surgery, Henry Ford Hospital, has developed an alimentation method of liquefying a full normal diet and adding high-calorie foods, which may be administered through a small-bore polythene tube.

dysphagia. Hyperalimentation causes regeneration of the mucous-membrane changes in this syndrome without intravenously administered iron or vitamins.

Two cases, 1 associated with rupture of the esophagus, are reported.

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PEPTIC ULCER*

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It is not uncommon to encounter a middle-aged patient who for a number of years has suffered from ulcer and who, weary of his recurrent trials, seeks relief in surgery. Physicians are now less reluctant to advise surgical treatment of refractive ulcers than they were before the introduction of antibiotics, and it is generally agreed that modern surgical treatment is more effective and less hazardous. Yet many are unaware of the progress in surgical treatment in the past two decades, and it seems appropriate to restate and re-evaluate results so that therapy can be advised in the light of contemporary knowledge.

In the treatment of persistent gastric ulcer few would disagree that resection should be advised because of the ever-present threat of cancer. Duodenal ulcer, with its various manifestations, calls for more subtle appraisement before treatment can be appropriately selected in a given case. Of great interest in this regard is a recent study, by Moore and his associates[1] at the Massachusetts General Hospital, of 1264 duodenal ulcers followed over a five-year period (1942-1946). It was found that in 738 patients treated medically the mortality was 2.03 per cent, whereas that in 175 patients treated by gastric resection was 2.86 per cent — a difference of no statistical significance. Relief of symptoms on complete rest in a hospital does not mean that a patient with peptic ulcer will be satisfactorily managed when he returns to his home and family and business. The authors noted greatly improved results in terms of medical and economic rehabilitation in patients treated surgically.

From this study it was concluded that surgery should be considered for patients with active ulcers with a history of perforation, of an acute hemorrhage or of progressive pain over a two-year period under a physician's care, or male patients with onset of symptoms at the extremes of life.

Five-Year Review of Surgical Results

One hundred and forty-six operations as definitive treatment of ulcer, exclusive of those for perforation, were performed at the Bridgeport Hospital from 1947 through 1951. Resections were done in 109 cases, gastroenterostomy and vagotomy in 19, gastroenterostomy alone in 12, and vagotomy alone in 6. There were 4 deaths. Two of these occurred several months after surgery, but since they were the direct result of operation, they were included. All 4 deaths were in the group resected. The over-all mortality was 2.7 per cent, and the mortality for resection was 3.6 per cent. This group included resections for massive bleeding and for marginal ulcer — cases often excluded from reported series of resections.

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The mortality figures compare favorably with those of other institutions throughout the country (Table 1).

The youngest patient was twenty-five, and the oldest eighty-six years of age. The average age was fifty-three and six-tenths years. This was three and a half years higher than the average age in the University of Minnesota series.

There were 58 operations for duodenal, and 43 for gastric ulcer. Eight operations were secondary, predominantly for recurrent or marginal ulcer after gastroenterostomy. Ten surgeons performed these operations.

The increasing number of resections in recent years is demonstrated in Table 2.

The indications for operation were the time-honored ones of persistence of gastric ulcer in spite of treatment and of hemorrhage, obstruction and prolonged disability for duodenal ulcer. The procedure was a radical resection, with a short-loop anastomosis performed either in front of or behind the colon according to the Polya or Hoffmeister method. Most, but not all, ulcers were removed with the specimen, and in all cases the antrum and two thirds to three fourths of the stomach were removed.

Table 1. *Mortality in Various Hospitals.*

Hospital	Period	Resections	Deaths	Mortality %
Massachusetts General[1] (duodenal ulcer only)	1942–46	175	5	2.86
Hartford[2]	1942–47	92	7	7.5
University of Minnesota[3] (duodenal ulcer only)	1940–49	893	44	4.8
University of Maryland[4]	1946–50	177	12	6.7
Bridgeport	1947–51	109	4	3.6

Table 2. *Types of Operation for Peptic Ulcer.*

Year	Resections	Gastroenterostomies	Vagotomies	Combined Vagotomies and Gastroenterostomies	Totals	Deaths
1947	3	2	3	5	13	1
1948	20	1	2	3	26	1
1949	19	5	0	1	25	2
1950	26	3	1	10	40	0
1951	41	1	0	0	42	0

Significant postoperative complications, including the fatal ones, occurred in 12, or 11 per cent, of the cases (Table 3).

There were 3 cases of recurrent ulceration, an incidence of 2.7 per cent. One of these responded promptly to medical treatment, and the patient has been asymptomatic for three years. Another was reresected, with cure, and the third had an abdominal vagotomy, with disappearance of the marginal ulcer on x-ray study. There were no complications or deaths among the patients treated by gastroenterostomy and vagotomy. The 8 secondary operations all consisted in taking down gastroenterostomies and resections of three fourths of the stomach. There were no deaths in this group. The increased mortality of secondary operations (9.7 per cent as reported by Glenn[5]) is a cogent argument in favor of radical resection at the primary operation.

Table 3. *Complications in Fatal Cases.*[a]

Age	Sex	Location	Year	Interval between Operation and Death	Autopsy	Complication
yr.						
50	M	Duodenum	1947	5 mo.	No	Three operations — inanition
57	M	Duodenum	1948	6 mo.	No	Pylephlebitis — liver abscess
69	F	Stomach	1948	14 days	Yes	Acute pericarditis
46	M	Stomach	1949	15 days	No	Peritonitis

[a] In 8 nonfatal cases the complications were as follows: obstruction of stoma, 2; duodenal fistula, 2; pancreatitis, 2; and hemorrhage from stoma, 2.

Material

Detailed analysis of patients operated on and followed by me is presented as a sample of the entire series. This group comprised 38 patients, of whom 32 had resections and 6 had vagotomy, with gastroenterostomy added in 2. The patients were seen monthly for three visits, then every three months for a year, and then at intervals of six months. There were no deaths.

Because of their relatively advanced age several patients presented systemic complications. Generalized arteriosclerosis was frequently noted. Two patients had had attacks of coronary thrombosis, and another had severe arthritis. One patient with a large prepyloric ulcer that failed to heal had bilateral fibrous tuberculosis. Other complications included severe hypertension, arrested carcinoma of the pyriform sinus and eventration of the diaphragm, in 1 case each. Another patient had chronic cholecystitis and cholelithiasis, and the gall bladder was removed in addition to gastric resection.

One patient had been operated on for kidney stones and explored elsewhere for parathyroid hyperplasia. It is interesting that patients with hyperparathyroidism tend to have peptic ulcers, and recently a case was reported by Albright[6] in which exsanguination from the duodenal ulcer occurred several months after surgical cure of the

endocrine disease. In an elderly woman with extensive bilateral varicose veins, prophylactic femoral-vein ligations were done at the time of gastrectomy.

Results of Vagotomy

Four of the 6 vagotomies were done six years ago, 1 five years ago, and 1 three years ago, all for duodenal or marginal ulcer. In each case the result has been completely satisfactory, with disappearance of pain, gain in weight or maintenance of normal weight, and absence of untoward side effects. Two patients, both elderly and 1 with heart block, had had gastroenterostomy ten years previously and had anastomotic ulcers. A transthoracic vagotomy was done on 1, and an abdominal vagotomy on the other after gastrotomy had disclosed a marginal ulcer. The 1 obstructed patient, a woman, had shortly before undergone a vulvectomy and bilateral dissection of groin and iliac lymph nodes for carcinoma. She has been completely well for six years after the operation for carcinoma and duodenal ulcer, is 20 pounds heavier and has been working regularly. The results in these 6 cases are shown in Table 4.

Table 4. *Results of Vagotomy.*

Age	Sex	Site	Year of Operation	Duration of Symptoms	Weight Gain	Result
yr.				yr.	lb.	
Transthoracic vagotomy alone:						
54	M	Duodenum	1947	18	26	Complete relief
56	M	Jejunum	1947	10	6	Complete relief
37	M	Duodenum	1948	4	None	No ulcer symptoms
Transthoracic vagotomy & posterior gastroenterostomy:						
30	M	Duodenum	1947	6	None	Complete relief
45	F	Duodenum	1947	5	20	Complete relief
Gastrotomy & abdominal vagotomy:						
62	M	Jejunum	1950	10	10	Complete relief

Two male patients with duodenal ulcer had transthoracic vagotomy alone. One of these had had impending perforation on two occasions. He has had no ulcer symptoms since vagotomy. The other, a patient with severe symptoms extending over a ten-year period, with excessive night secretion of hydrochloric acid, has gained 20 pounds in weight and is asymptomatic in spite of overindulgence in cigarette smoking and grossly irregular sleeping and eating habits. None of these patients have had any of the side effects usually described as accompanying vagus section. It is my impression that vagotomy, when used judiciously, is unquestionably an adjunct in the definitive treatment of duodenal and marginal ulcer.

Gastric Resection

The average age of the 32 patients (29 males and 3 females) treated by resection was fifty-six years, or five and nine-tenths years older than those in the University of Minnesota series, and two and four-tenths years older than the average of those in the Bridgeport Hospital series. Sixty-five per cent were over fifty years of age. Six of these patients had previously been operated upon for perforation, and 6 had a high degree of obstruction.

Sixteen had duodenal, and 12 gastric ulcer, 2 marginal ulcer, and 1 both gastric and duodenal ulcers. One patient had an obstructing esophagitis after a gastroenterostomy done elsewhere for duodenal ulcer. Ten of these patients had had symptoms for eight to forty years, the average duration of the disease in this group being sixteen and eight-tenths years.

Cancer was the definite preoperative diagnosis in 4 of the 12 gastric ulcers. In 2 patients ulcers on the lesser curvature of the stomach failed to heal after five weeks of medical treatment in the hospital; both proved to be benign. Another lost a great deal of weight and had severe secondary anemia, with a large ulcer crater on the lesser curvature diagnosed as cancer on x-ray examination. At operation a perforation into the liver, with a localized liver abscess, was found to be associated with a benign ulcer. In the fourth case, an eighty-one-year-old woman, the presence of a tangerine-sized, discrete mass in the epigastrium made cancer seem likely, and yet a benign ulcer was found. These cases serve to emphasize the frequent inaccuracy in diagnosis of gastric lesions.

Massive Bleeding

Resection was performed in 6 cases for massive hemorrhage (Table 5), but no patient was operated upon as an emergency within the first few hours of admission as advocated by some surgeons. In all cases blood transfusions were given, and x-ray studies carried out to determine the cause of the bleeding.

Table 5. *Data in 6 Cases Associated with Hemorrhage.*

Age*	Sex	Red-Cell Count†	Total Blood Loss	Location of Ulcer	Interval between Admission and Operation
yr.					days
48	M	2,120,000	7,500	Duodenum & stomach	20
65	M	2,800,000	10,000	Stomach	28
56	M	2,900,000	3,000	Stomach	7
53	M	2,880,000	3,000	Jejunum	18
74	M	2,480,000	3,500	Duodenum	13
81	F	2,170,000	3,500	Stomach	13

*Average, 63 yr.
†Average, 2,570,000.

All had relatively uncomplicated postoperative courses, and it is believed that these patients are

best treated by blood replacement and elective surgery after a specific x-ray diagnosis has been made. The rare patient who continues to bleed can be operated on immediately when it becomes apparent that such a situation exists.

High Gastric Ulcer

High gastric ulcers can be successfully treated by the Madlener procedure, as advocated by Colp.[7] This operation consists in resection below the ulcer, a large part of the acid-secreting portion of the stomach thus being removed. This procedure was used successfully in 1 case in which the patient, a slightly built man who weighed only 117 pounds, was a particularly finicky eater (Fig. 1). It was feared that removal of three fourths of the stomach would create a serious nutritional problem.

FIGURE 1. *Preoperative X-ray Appearance of a High Gastric Ulcer.*

The stomach was opened, and the ulcer inspected. It was 1.5 cm. in diameter, sharp edged and without induration. Although the lesion was obviously benign, a biopsy was taken, and frozen section showed no malignant degeneration. About two thirds of the stomach was removed, the ulcer being left in situ. The ulcer healed in two weeks according to x-ray criteria; the patient has remained asymptomatic for three and a half years and is 2 pounds heavier. An x-ray film of the stomach is shown in Figure 2. The danger in this procedure lies in the possibility that such an ulcer, even though benign in appearance and on biopsy, is malignant. It is therefore not advisable for extensive use.

Delayed Resection

One patient, seventy-two years of age, had a perforation of a gastric ulcer. It was closed and because of a history of a previous cancer elsewhere in the body, the stomach was resected ten days later. Another patient bled steadily for two weeks after closure of a duodenal perforation. When resection was performed the duodenal ulcer was found to be healed, and the bleeding was from a large gastric ulcer. These were the only patients with recent perforations who were reoperated on shortly after closure of the perforation.

Edwards[4] reports 8 cases in which emergency resection was performed for perforation, and Auchincloss[8] describes 13 similar cases, with no deaths.

FIGURE 2. *X-ray Appearance of the Stomach Three and a Half Years after Resection below the Ulcer.*

Delayed resection after perforation has also been advocated.[9] One questions the wisdom of extensive use of emergency and delayed resections in view of the fact that 54.7 per cent of 62 patients with acute perforations in the series of Moore et al.[1] were completely well or asymptomatic on an ulcer regimen after simple closure. It is also to be noted that the mortality of perforation with simple closure is still 11.5 per cent,[10] and it is doubtful if resection would reduce this percentage.

Constricting Esophagitis

Another patient, a sixty-four-year-old man, had had a gastroenterostomy at another hospital in 1944 for duodenal ulcer with obstruction. Two months after operation he was unable to swallow anything but liquids because of obstructing esophagitis (Fig. 3). He was treated with esophageal dilatations at another institution and was then

FIGURE 3. *X-ray Film, Showing Narrowed Lumen of Lower Esophagus and Gastroenterostomy.*

able to take a soft diet, only to have the obstruction, even for liquids, recur. Finally, monthly dilatations were necessary.

Stimulated by the report of Wangensteen and Leven[11] of alleviation of constricting esophagitis by gastric resection, I offered this procedure to the patient, who accepted. (Wangensteen believes that esophagitis is a manifestation of the ulcer diathesis and caused by the regurgitation of gastric juice into the lower esophagus; it should therefore be relieved by radical gastric resection.) In 1950 this patient was operated on, the gastroenterostomy taken down, and a high resection done. In the early postoperative period he began to eat, first soft foods and then solids, and he has continued to do so for three years without difficulty. X-ray films at first showed considerable scarring and narrowing of the lower third of his esophagus, but recent films demonstrate a normal-appearing lower esophagus (Fig. 4). Wangensteen advised esophageal dilatation after resection. This patient, however, refused to permit dilatation, and his esophagus returned to its normal caliber without it.

Evaluation of Results

Three of the 32 patients resected have died of other causes — 1 of pneumonia at eighty-one, 1 of pulmonary tuberculosis at fifty-four, and 1 of cerebral hemorrhage at fifty-six years of age. One patient moved to a distant city. Twenty-eight were personally interviewed and questioned minutely regarding digestive disturbances, food idiosyncrasies and ability to work and to gain weight.

A recurrent ulcer developed in the stomach pouch in a fifty-four-year-old man with a history

FIGURE 4. *X-ray Appearance of the Esophagus after Gastric Resection in Patient Shown in Figure 3.*

of ulcer of fifteen years' duration who had been operated on in 1948 for pyloric obstruction. The gastroenteric stoma failed to function, and at reoperation the efferent loop was found kinked and pulled up through the opening in the mesentery of the transverse colon. The kink was freed up with some difficulty, and the stoma felt to be patent. As an additional safeguard a jejunojejunostomy was done. One year later the ulcer of the gastric pouch developed. This healed promptly on an ulcer regimen and has remained healed to date. This sole temporary recurrence cannot be con-

sidered a poor result of resection but must be attributed to diversion of the alkaline contents away from the stoma by the jejunojejunostomy.

Two patients reported intolerance to ice cream and milk, and 1 of these, in the early postoperative period, felt weak, drowsy and dizzy with palpitation after eating, and had to lie down until these symptoms subsided. These effects were found to be related to overloading the stomach and did not occur when the patient limited the size of his meal.

A third of the patients (10) found that they were unable to regain their average preoperative weight — that is, what they had considered to be their normal weight over a number of years before operation. These patients averaged 10 to 15 pounds below their assumed normal weight. This was the dominant undesirable effect of gastric resection in this group of cases as well as in other series reported.

In the first month or two after operation about half these patients undergo a period of adjustment during which they learn how much their stomachs will comfortably hold. All patients resected must be informed that they should eat frequently to compensate for their limited capacity, and as time passes most of them establish eating habits that are completely satisfactory. Patients who remain underweight are commonly classified as imperfect results of gastric resection for ulcer. Although an ideal weight is preferable to being underweight, overemphasis on this factor casts an unkindly light on an extremely satisfactory procedure. Underweight people in the general population are not regarded as being unduly handicapped. Hence a moderate reduction in weight should not be a prohibitive price to pay for cure of an undermining and potentially fatal disease. Two thirds of the patients in this group have had no difficulty in maintaining their normal weight.

All patients have returned to their usual occupations, most of them within a month or six weeks of operation. Only 1 patient believes that he was not helped by gastric resection. This man, now seventy-nine years old, is working daily at his trade as cabinetmaker. He had a prepyloric ulcer that failed to heal after medical treatment for five weeks in the hospital. His only complaint is that his weight fluctuates from 15 to 20 pounds under his preoperative weight of 158.

All others have expressed satisfaction with the results of operation, and many have stated that they regret not having been operated on many years earlier. The absence of pain and the ability to take a varied diet without fear have been generally greatly appreciated. This is in accord with the findings of Rauch[3] in his evaluation of the University of Minnesota series. He reported that 90 per cent of 702 patients considered themselves benefited by surgery — a considerable number of whom "went into a prolonged and elaborate dissertation concerning the magnitude of their appreciation."

Discussion

In a recent review from the gastrointestinal clinic of the Beth Israel Hospital in Boston Banks and Zetzel[12] noted that 8, or 16 per cent, of 48 patients with the diagnosis of gastric ulcer subsequently died of verified carcinoma of the stomach. In addition, only 11 patients, or 23 per cent, were free of ulcer symptoms during the follow-up period. The authors conclude that surgery "may be the only direct and practical answer to the problem for most cases."

Ravdin and Horn[13] point out that errors are made in diagnosis not only by the clinician but also by the roentgenologist and even by the surgeon and pathologist in the operating room on gross inspection of the stomach. At the University of Pennsylvania Hospital gastric ulcers are treated without delay by gastric resection. This attitude was also held by Lahey,[14] who believed that if medical treatment is elected for a gastric ulcer the patient should be told that he has a 15 per cent chance of having cancer. Kirschner and Garlock[15] have stated, "it seems quite clear that the risk of overlooking an early gastric cancer by treating a supposed gastric ulcer by medical means is far greater than the risk of a gastrectomy for a benign ulcer under modern conditions."

Duodenal ulcer is rightly considered primarily a medical problem. Yet in chronic or recurring ulcers the alert physician would do well to think of surgical treatment as a valuable and definitive accessory in the care of the disease and not merely as the only recourse when life is threatened by massive hemorrhage or acute perforation. With the mortality of definitive treatment under 5 per cent today, too conservative an attitude exposes the patient to unnecessary risk and disability.

Summary and Conclusions

One hundred and forty-six cases of peptic ulcer treated surgically at the Bridgeport Hospital from 1947 through 1951 are reported. One hundred and nine were treated by gastric resection, with a mortality of 3.6 per cent. The remainder were treated by gastroenterostomy and vagotomy, or by vagotomy alone.

A series of 38 patients operated on and followed by one surgeon is evaluated for end results. There were no deaths in this series.

Uniformly good results were achieved in the 6 patients treated by vagotomy.

In the 32 patients treated by resection there was 1 recurrent ulcer of the stomach pouch that has remained healed for three years after medical treatment.

A third of the resected patients remained 10 to 15 pounds under their preoperative weight. All returned to their previous occupations. All but 1 were satisfied with the results of operation.

It is reiterated that persistent gastric ulcer should be considered a surgical disease.

The indications for surgery in duodenal ulcer should be more stringently drawn to avoid the serious complications of protracted disease.

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AN EVALUATION OF THE INFLUENCE OF DL-METHIONINE TREATMENT ON THE SERUM LIPIDS OF ADULT AMERICAN MALES*

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STUDIES with monkeys have revealed that hypercholesterolemia and subsequent vascular lesions are produced in this primate species if the animals are given a diet deficient in the sulfur-containing amino acids cystine and methionine and at the same time receive large amounts of cholesterol in the diet.[1] Also in this species, as well as in rats and mice, either dietary supplements of cystine or methionine or protein rich in these amino acids will largely prevent the anticipated hypercholesterolemia and will reverse the existing abnormality produced by such procedures.[2] The data of dietary surveys done by two groups of workers indicate that DL-methionine may be a limiting nutrient in the diets of the American citizens studied.[3, 4] This information, taken with the large prevalence of hypercholesterolemia and atherosclerosis among the population, suggested the desirability of assaying the influence of methionine supplements upon the serum lipids in a selected group of American males, and it is these data that make the substance of this brief report. No influence of methionine supplements on the serum lipids was demonstrated.

Methionine, either singly or in combination with other of the so-called lipotropic substances, has been widely advocated as a treatment for atherosclerosis in human beings. Sound evidence to justify this procedure is lacking. Herrmann[5] has presented evidence that methionine supplements in the food of old hens with cholesterolosis diminished the cholesterol in the liver and aorta when compared with a control group of birds. He[6] and others[7] have also concluded that either methionine or choline was effective in lowering serum cholesterol of patients or in preventing the progression of the clinical manifestations of atherosclerosis. Since excessive liver lipid depositions are not a characteristic of human atherosclerosis, the notion that the lipotropic action of methionine, which has been demonstrated in certain carefully contrived animal experiments, will be beneficial in the management of human vascular disease is illogical.

Plan of Experiment

A population of 112 adult males was available. The group was composed of members of the faculty of Massachusetts Institute of Technology. These men were actively engaged in teaching and research. During the previous twelve months each of these men had undergone a routine physical examination in the health service of the institution, and at that time blood was obtained for measurement of the total serum cholesterol and lipoproteins of the S_f12-20 and S_f20-100 classes.¶ From this

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¶The β lipoproteins of serum are characterized and measured according to their rate of movement in a field of force created in an ultracentrifuge. Since the lipid content of lipoprotein molecules buoys them up, they tend to float when suspended in an appropriately adjusted salt solution. The conventional sedimentation unit, the Svedberg (S), describes the rate of sedimentation of molecules more dense than their surrounding medium. Gofman et al.[8] have applied this same constant but with an opposite sign to the characterization of lipoproteins and have devised the symbol S_f to indicate the flotational properties of these molecules. Molecules that are described as S_f12-20 are thus all those which flotate with a rate of 12 to 20 times 10^{-13} cm. per second per dyne per gram. The division of classes of lipoproteins is arbitrary although by convention they are generally divided as S_f0-12, 12-20, 20-100, 100-400 and 400 and above.

group a sample of 26 men was selected representing all those with a level of the S_f12-20 class of lipoprotein of 50 mg. per 100 cc. or more. These were invited to participate in the study, and 24 men accepted. Two samples of blood for control measurements were obtained with an interval of one week. The subjects were then given a supply of DL-methionine in 0.5-gm. capsules* and instructed to ingest two of these capsules three times daily, thus furnishing 3 gm. of methionine a day. They were asked to continue their daily routine of activities and diet without change. The methionine supplementation was continued for forty-two days. Additional blood samples were obtained at intervals of two, four and six weeks after the beginning of the methionine supplement. After the bleeding at the sixth week, the supplements were stopped, and the final sample of blood was obtained two weeks later. The total serum cholesterol was measured by the method of Abell and her associates,[9] and the serum lipoproteins by that of Gofman et al.[8]

Results

A statistical summary showing the means and standard deviations for each serum lipid quantity

Table 1. *Mean Values and Standard Deviation of Certain Serum Lipids of a Selected Group of 24 Males Treated with 3 Gm. of DL-Methionine Orally for Forty-Two Days.*†

Time Interval	S_f 12-20	S_f 20-100	Total Cholesterol
	mg./100 cc.	mg./100 cc.	mg./100 cc.
First control	59.5 ±17.6	118.3 ±57.4	273.0 ±60.9
Second control	61.8 ±23.3	102.6 ±49.5	269.0 ±62.2
Two wk. of methionine treatment	61.5 ±19.2	111.1 ±55.5	263.6 ±60.1
Four wk. of methionine treatment	68.3 ±26.2	108.5 ±53.6	259.6 ±57.7
Six wk. of methionine treatment	63.0 ±17.5	112.7 ±82.3	268.7 ±66.1
Two wk. after completion of treatment	61.3 ±25.8	100.0 ±62.4	281.0 ±66.7

†The mean values are followed by standard deviations of the distributions.

and at each time interval is presented in Table 1. The differences of means for all 24 subjects at each bleeding were tested by the application of Student's "t" test, and no differences not readily attributable to chance could be found. Inspection of either composite or individual curves relating the level of each lipid quantity to the phase of the experiment gave no evidence of significant trends or any other indication that the methionine supplements had altered the status of the serum lipids.

*This material was generously supplied by the Upjohn Company, Kalamazoo, Michigan.

Discussion

There is no evidence from this experiment that the serum lipids of these subjects were influenced by relatively large amounts of supplementary methionine. There is some indication, largely adduced by Leary,[10] that atherogenesis is a sporadic event of relatively short duration with long quiescent periods intervening. It might be admitted that this eight-week period of observation of 24 men did not chance to reveal such an event or alternatively that such events were prevented from occurring by the treatment. Since untreated controls were not used in this experiment, the latter possibility cannot be evaluated. However, we have followed 65 adult males over ten-week periods of observation with two bleedings each week in the course of another study and have never seen sudden and sporadic increases of serum lipids.[11] From this evidence, sporadic and short-lived hypercholesterolemia seems to us improbable.

Summary

Twenty-four American males with moderate to marked elevations of the serum cholesterol and of several classes of lipoprotein were continued on their usual diet and given 3 gm. of methionine daily in three equal doses at mealtime for six weeks. This treatment did not alter the serum cholesterol and lipoprotein levels.

The co-operation of the experimental subjects in this study, which is gratefully acknowledged, was so outstanding that it deserves comment. A pitfall in any evaluation of an oral treatment, especially one done on an ambulatory basis, is the uncertainty that the medication was taken. The present study was spared this defect by the co-operation of the subjects, who were themselves aware of and in many cases engaged in problems of experimentation.

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MEDICAL PROGRESS

NEEDLE BIOPSY OF THE LIVER. I. ITS USE IN CLINICAL AND INVESTIGATIVE MEDICINE*

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THE increasing use of needle biopsy of the liver clearly indicates its wide acceptance as a clinical and investigative tool. More than 20,000 biopsies have been reviewed, and it is now possible to reassess the usefulness and limitations of the procedure.

A few conclusions appear to be warranted. Needle biopsy is not necessary for correct diagnosis of most cases of liver disease. It is indispensable, however, in a small but important group. It is also helpful in treatment and prognosis by defining the stage of known disease. Judicious use, based on a broad understanding of liver disease, is accompanied by a minimal morbidity and a negligible mortality; less discriminate use by high morbidity and disastrous mortality.

METHODOLOGY

The various methods of liver biopsy, which have been discussed elsewhere,[1-17] are not reviewed here. Briefly, the procedure consists of the introduction into the liver of a long needle, which severs a core of tissue, measuring 1 or 2 mm. in width and 1 to 3 cm. in length. It is relatively simple and can be performed at the patient's bedside under local anesthesia. The patient lies either on his back or on his left side, and the needle is introduced through the anterior abdominal wall below the right costal margin, or through the right lateral chest wall, depending on the size and position of the liver. The entire procedure may be accomplished by a single operator ten minutes or less after the patient has been prepared.

Several different needles are used: some (Iversen and Roholm,[8] Baron,[1] Gillman,[4] Terry,[10] Franseen[15] and the Roth-Turkel[14] modifications) permit the application of suction through a syringe attached to the needle hub. The Silverman[12, 16] needle employs a different principle: a bi-pronged needle grasps and without suction severs a core of tissue within a cannula. Herrera[17] has attached a thin wire loop to the distal end of the needle that severs the base of the liver core from the liver mass. The Roth-Turkel needle provides a larger specimen than the Silverman needle. The needles and necessary adjuncts such as syringe, hypodermic needles and scalpel blade for nicking the skin may be sterilized in a small, compact parcel and carried in the pocket to the bedside. Preoperative sedation, such as meperidine hydrochloride, is usually recommended.

The obtaining of a satisfactory specimen depends on many factors, including the experience and skill of the operator, the size, position and consistence of the liver, the co-operation of the patient and the type of needle used. So accurately may the liver be localized by percussion that even small non-palpable livers can be successfully biopsied.§ Using the Vim-Silverman needle, Schiff[18] reported only 4.8 per cent failures in 700 patients, compared with an earlier report of 40 per cent by Hoffbauer.[5] Sherlock[9] had 10 per cent failures in her first 126 attempts with a suction-type needle but reduced this to 2 per cent in the subsequent 138 trials. Failure to obtain tissue occurs more frequently with hard, fibrous livers.

VALIDITY OF THE BIOPSY SPECIMEN AS A REPRESENTATIVE SAMPLE[19-33]

The normal liver is composed of morphologically identical lobular units, all subserving identical functions, as far as is known. The average biopsy specimen contains 5 to 20 lobules and, accordingly, samples generalized anatomic change. For example, complete obstruction of the common bile duct is reflected anatomically by evidence of bile stasis in all segments of the biliary system from the small intercellular bile canaliculi to the large bile ducts. Virtually all lobules are involved by diffuse metabolic alterations such as nutritional fatty liver, hemosiderosis, hemochromatosis, portal fibrosis and glycogen-storage disease. This is also true of generalized diseases like hepatitis of the epidemic, toxic and serum varieties,[3, 33] malaria, leukemia and some lymphomas.[4] Mallory[6] showed by means of multiple liver sections the diffuse nature of the anatomic lesions of very early hepatitis in soldiers killed accidentally. The liver appears to be diffusely involved by the granulomatous lesions of tuberculosis,[34] sarcoid[35] and brucellosis.[36] Waldstein[37] took 10 biopsy samples from each of 15 patients with cirrhosis,

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§Recently, one of us successfully biopsied without complication a non-palpable liver that weighed less than 600 gm. at autopsy several weeks later.

toxic hepatitis, and passive congestion, and noted uniformity in liver-cell injury and fat, and only 10 per cent discrepancy in lobular pattern, scarring and inflammation. Numerous studies of repeated liver biopsies in human beings with fatty liver have shown consistent decreases in the quantity of stainable lipid correlating well with the improved clinical course of the patients studied.[38-42] This could not have occurred without a uniform distribution of fat within the liver.

The uniform distribution of chemical constituents of the liver has been reported in several diseases. Iversen and Krarup[44] showed that in experimentally produced fatty liver of pancreatectomized dogs, the quantity of fat in the various lobules was so uniform that a microscopic sampling permitted a quantitative estimate of the total fat content. Similarly, the histologic estimate of the amount of fibrous tissue in small liver fragments (somewhat larger than that obtained in the usual liver biopsy) provides a reliable index of the amount of collagen determined chemically in the same specimen, even when fibrosis is extensive.[30] Rourke and Stewart[45] analyzed livers of 12 patients dying of cerebrovascular accidents, diabetes, cirrhosis and ulcerative colitis, and demonstrated the uniform distribution of water, fatty acids and total and esterified cholesterol in 5 to 12 samples of each liver. Vitamin A distribution was less uniform, but the method used for this determination had a 20 per cent error.

The sampling error of the biopsy method is often overemphasized. Localized diseases such as cancer, infection and abscess may not always be satisfactorily sampled by a single specimen; yet the correlation between biopsy and autopsy diagnosis has been high in most cases. Giesen et al.[46] noted essential agreement in 47 out of 48 cases; the biopsy picked up 25 of the 26 focal lesions as well as all 22 of the diffuse lesions. Molle and Kaplan[47] found the biopsy diagnosis correct in 85 per cent of patients subsequently examined at operation or at autopsy. Wagoner[39] demonstrated exact correlation in 73 of 84 cases, including 20 of 30 focal lesions. The only diffuse lesion not detected by biopsy was minimal early cirrhosis. Nine of the focal lesions were neoplastic, and 1 was gummatous.

Focal lesions may not cause symptoms of liver disease until they are widespread. This may account in part for the relatively high percentage of successful biopsies in focal conditions.

In summary, it appears that the needle-biopsy specimen accurately samples all diffuse anatomic lesions and the majority of focal lesions. The finding of a positive specimen is highly significant, whereas a negative or normal specimen excludes the presence of diffuse hepatic but not focal disease.

Comparison with Other Biopsy Procedures

Biopsy performed at laparotomy provides the most reliable method for sampling isolated lesions, since the surface of the liver may be examined, the site of biopsy selected, and a relatively large specimen of tissue obtained. Womack[48] performed wedge biopsies of the liver under local anesthesia through a 5-cm. abdominal incision. Mateer et al.,[49] comparing surgical wedge biopsy with needle biopsy, reported that the specimen obtained surgically regularly contained more fibrous tissue than that obtained by needle. It is believed by many pathologists that the subcapsular fibrous tissue may not be a true reflection of the fibrous-tissue content of the liver generally.[50] We and others have noted that pathological specimens of liver obtained surgically after the completion of operations on the upper abdomen regularly manifest a variety of changes, including hemorrhage, inflammation, infarct and necrosis.[51, 52] Since liver tissue obtained at the beginning of operation was free of such acute changes it is clear that these changes were caused by the operation itself. Furthermore, specimens taken at the site of marked retraction or after prolonged manipulation of the liver showed the greatest changes. Failure to appreciate these artefacts has led some authors to attribute undue significance to them.[49]

Peritoneoscopic biopsy has been used with success by several workers, including Benedict,[53, 54] Ruddock,[55] Kalk, Brühl and Sicke,[56] Keil et al.,[57] Hoffbauer[58] and McHardy and his associates.[59] Like exploratory laparotomy, peritoneoscopy permits examination of the liver surface and the selection of the biopsy site. Since the peritoneoscopic forceps biopsy is limited to the edge of the liver where tissue changes may not be representative of the entire organ, some workers have preferred to use needle biopsy in combination with peritoneoscopy. McHardy, Browne and Edwards[59] found the combined technic to yield accurate diagnoses in 96 per cent of cases, whereas clinical diagnosis alone was accurate in only 56 per cent. Benedict[53] reserves the use of needle biopsy under direct peritoneoscopic view for cases in which the liver capsule is exceedingly tough. Hoffbauer,[58] after using peritoneoscopy as a diagnostic procedure for several years, has discontinued its routine use in favor of the simpler bedside needle biopsy. He states that the advantage of peritoneoscopy over laparotomy afforded by the small abdominal incision and the permissible early ambulation has been diminished in recent years, since rapid ambulation has been permitted postoperative patients. Furthermore, distress followed peritoneoscopy in about 1 out of every 5 patients, frequently with rebound tenderness and elevation of white-cell count. Diffuse abdominal pain and moderate ileus sometimes persisted for days, owing to the necessary creation of a tense pneumoperitoneum. These complications increased the difficulty of recognizing serious intraperitoneal bleeding or inflammation after biopsy. Hoffbauer now reserves the use of the peritoneoscope for

patients with ascites, who are seldom candidates for surgical therapy and who tolerate the procedure well.

Needle biopsy has many practical advantages: the apparatus is simple and inexpensive, a minimum of preparation is required, and the procedure may be performed at the patient's bedside; the necessary time, facilities and technical assistance are insignificant compared to those usually required by the alternative methods of biopsy. The operation itself is associated with less pain to the patient, and uncomplicated recovery is the rule. The performance of multiple biopsies minimizes its diagnostic error in focal lesions. Several biopsies may be performed when necessary, with little or no objection from the patient. For these reasons peritoneoscopy and laparotomy performed solely for diagnostic liver biopsy have been replaced largely by bedside needle biopsy.

Early Diagnosis of Liver Disease

The symptoms of liver disease are nonspecific: loss of appetite, "indigestion," nausea, vomiting, vague distress or pain in the upper abdomen, malaise, diarrhea and so forth occur in numerous disturbances of the gastrointestinal tract and other organs.[58, 60, 61] The liver may be palpable in normal persons and in those with emphysema. Patients with infectious hepatitis,[62, 63] infectious mononucleosis,[64] advanced cirrhosis or metastatic cancer may give no signs referable to the liver despite unequivocal morphologic evidence of damage to the liver. Overt signs such as jaundice, spider angiomas, hepatosplenomegaly and ascites are usually evidence of advanced disease.[65] But even these findings may be caused by disease of other organs. Ascites, for example, occurs in congestive heart failure, intra-abdominal cancer, chronic peritonitis, renal disease, myxedema, benign ovarian tumors and other conditions.

The use of liver-function tests helps recognition of latent or early impairment of function. Although some of these tests, like the bromsulfalein retention and the cephalin cholesterol flocculation, afford relatively sensitive screening, they often fail to correlate with liver morphology.[66-75] Abnormal values of bromsulfalein retention, especially difficult to evaluate in obese, aged, bleeding[76] and febrile patients,[77] may not always warrant assumption of the presence of liver disease. Similarly, hepatic disease cannot be excluded on clinical or functional grounds. Neefe,[61] Sherlock[78] and others have described the persistence of symptoms in patients convalescing from chronic hepatitis despite negative function tests. Biopsy was an effective means for distinguishing the psychogenic from the organic origins of these symptoms. Hult[58] also found significant amounts of fat in the livers of such patients.

Many dissimilar pathologic processes involving the liver give rise to similar or identical clinical and laboratory findings. Despite 97 liver-function tests devised for the measurement of at least 77 liver functions in which 5000 chemical reactions are asserted to participate,[79] not a single disease can be diagnosed with certainty by the use of these tests alone. The liver participates as a sort of screen in widespread diseases of the body, especially those involving the blood, the gastrointestinal tract and the reticuloendothelial system. Hepatic biopsy may disclose the presence of such systemic disease. The morphologic method provides the only accurate means for recognizing most of the 200 pathologic entities that may involve the liver. In every hospital there are patients whose serious illness remains undiagnosed despite prolonged clinical and laboratory study. There may be no clinical findings to suggest liver disease. Yet liver biopsy, performed even in the absence of hepatomegaly, has proved useful in such cases. Von Falkenhausen et al.[80] recommend the use of liver biopsy in all cases of obscure illness in which a definite and clear diagnosis cannot be made by ordinary methods.

In addition to the more common diseases such as cirrhosis,[81] fatty liver, metastatic cancer, hepatitis[82] and obstructive jaundice, those diagnosed with the aid of biopsy include amyloidosis,[2, 9, 11, 13, 23, 83] Gaucher's disease,[84] Wilson's disease,[85-88] hemochromatosis,[11, 13, 89, 89, 90] syphilitic cirrhosis,[91] cardiac sclerosis,[9, 11, 13, 27] granulomatous diseases,[29] such as tuberculosis,[34, 89, 92, 93] leprosy,[94] brucellosis,[30, 95] sarcoid[13, 35, 96-98] and fungous infection,[99] inflammatory diseases such as infectious mononucleosis,[64, 98] Weil's disease,[64, 98] and toxic hepatitis from cinchophen,[99] chloroform[13] and arsenic[9, 99] poisoning, certain focal necroses such as tularemia,[98] syphilis,[98] liver abscess, both bacterial and amebic,[89, 94, 95, 100] periarteritis nodosa,[98] lupus erythematosus,[22] leukemia,[94, 98] Hodgkin's disease[98] and other lymphomas,[13] congenital cystic disease[96] and parasitic diseases, including ascariasis,[98] hydatid disease,[94] kala-azar[9, 94] and schistosomiasis.[13, 66, 98]

It is apparent that successful diagnosis requires well trained pathologists experienced in interpreting small fragments of tissue. Van Beek and Haex[28] and Popper[101] pointed out the histologic difference between the biopsy specimen and that obtained at post-mortem examination. Delay in fixation may obscure characteristic findings. This is particularly true in infectious hepatitis and in subacute atrophy, in which rapid autolysis may take place.[28] Deutsch and MacMahon[20] described the wide variation of histology in infectious hepatitis. Dible et al.[3] stated that the epidemic, arsenic and serum varieties of hepatitis cannot be distinguished histologically. The lesions of obstructive jaundice are sometimes difficult to distinguish from those of hepatitis. The finding of bile stasis alone does not always warrant unequivocal diagnosis of extrahepatic biliary obstruction, because focal bile stasis may be found in many nonsurgical conditions, including alcoholic and postnecrotic cirrhosis, hepatitis, fatty liver and cancer. The type of cirrhosis may not always be

determined on examination of a single specimen. Mallory[25] reported many years ago that it may be quite impossible to classify as many as 20 per cent of the cirrhoses even with the advantage of many sections obtained from the entire liver at autopsy. It is sometimes difficult to distinguish regenerative hyperplasia from primary carcinoma.[31] When there is insufficient tissue, the finding of apparently normal liver lobules may not warrant the diagnosis of "normal liver" because the tough portal fibrous tissue of a cirrhotic liver may be left behind. The experienced pathologist recognizes these limitations and may recommend rebiopsy when the diagnosis is not clear cut.

In clinical practice needle biopsy is universally recognized as indispensable for the most accurate diagnosis of liver disease. Schiff[18] found needle biopsy useful in 71.8 per cent of 574 biopsies performed on 500 patients. Biopsy confirmed the clinical diagnosis in 49.8 per cent, corrected an erroneous clinical diagnosis in 19.6 per cent and revealed unsuspected disease in 2.4 per cent. It provided no aid to diagnosis in 28.2 per cent because of inadequate specimen (6.8 per cent), noncontributory findings (18.4 per cent) and misleading findings (3 per cent). In 41 jaundiced patients mistaken diagnoses were rectified by needle biopsy. The mistaken diagnosis of metastatic carcinoma was made on 16 patients subsequently shown by biopsy to have non-neoplastic lesions. Clinical diagnosis was erroneous and corrected by biopsy diagnosis in 17.9 per cent of 112 patients with cirrhosis, 14.6 per cent of 82 with hepatitis and 9.8 per cent of 41 with liver neoplasm. These diagnostic errors were made at a clinic where liver disease is frequent and where it has been actively studied for many years by an experienced group.

A similar experience was recorded by Berk and Shay,[67] who found that 26.6 per cent of diagnoses based on complete history, physical examination and general laboratory and special liver-function tests, as well as x-ray examinations, were changed after needle biopsy. Moyer and Wurl[108] reported that 30 per cent of cases diagnosed as portal cirrhosis on clinical grounds were actually fatty metamorphosis without fibrosis on biopsy. In only 4 of 10 patients with clinical diagnoses of chronic hepatitis was this disease morphologically proved.

Differentiation of "Medical" from "Surgical" Jaundice

Adequate clinical and laboratory evaluation suffices to distinguish extrahepatic biliary obstruction from primary parenchymatous disease in most jaundiced patients. Gall and Schiff[93] estimate that in approximately 15 per cent of jaundiced patients, however, exact clinical diagnosis cannot be made. In the past it has been common practice to observe such patients for a more or less prolonged period in the hope that the correct diagnosis might become apparent.[109] Whereas clarification did occur in some cases, others became increasingly complex with time. With deepening jaundice undue procrastination is hazardous since progressive hepatic damage may occur if obstruction of the biliary tract is not relieved. On the other hand, unwarranted laparotomy in patients with hepatitis or cirrhosis is accompanied by a high mortality. It is in such cases that needle biopsy may be necessary.

The most experienced groups attest to the value of needle biopsy in the differential diagnosis of jaundice. Schiff[18] reported that an incorrect clinical diagnosis of the cause of jaundice was corrected by biopsy in 7 of 34 cases (20.6 per cent) of obstructive jaundice, and in 12 of 82 cases (14.6 per cent) of hepatitis, 7 of which had been diagnosed clinically as obstructive jaundice. In this small group alone it may be assumed that the 7 patients with obstructive jaundice requiring surgery would not have been explored, or at least operation would have been delayed, whereas 7 other patients with hepatitis would have been operated on erroneously. In the same study, Schiff pointed out that the mistaken diagnosis of metastatic carcinoma had been made on 3 patients with obstructive jaundice. In a series of 1146 patients seen in a medical clinic, Bjørneboe et al.[106] found that it was not possible to tell medical from surgical jaundice in 46 despite thorough clinical and laboratory study; biopsy was useful in 4 per cent of medical and 15 per cent of surgical patients with diseases of the liver, biliary tract and pancreas. The decision whether or not to operate was made correctly on the basis of liver biopsy in all but 4 of these cases. Lipp, Lenzner and Aaron[103] reported that exploratory laparotomy proved to be unwarranted in 10.8 per cent of their jaundiced patients. Several authors have emphasized the difficulty of assessment of jaundice in elderly patients.[21, 103] The place of needle biopsy has been well summarized by Krarup[7] as follows:

> It has not been possible by means of the biopsy method completely to eliminate the element of uncertainty in the differential diagnosis of cases of protracted jaundice. The employment of biopsy of the liver in connection with a careful anamnesis and objective examination, and a successful combination of liver function tests has reduced the element of uncertainty in doubtful cases more than was possible formerly.

Since clinical diagnosis in liver disease can only be presumptive, liver biopsy is indicated in any case of jaundice in which some degree of uncertainty exists.

The histologic characteristics of the liver in obstructive jaundice[100, 107] and in infectious hepatitis[3, 8, 30, 99, 107] usually permit ready differentiation. Certain apparently nonsurgical cases of jaundice are difficult to distinguish morphologically from extrahepatic biliary obstruction.[103] These include cholangiolitic hepatitis,[100] cholangiolitic biliary cirrhosis[110] and jaundice after methyl-testosterone therapy.[111, 112] Bjørneboe et al.[106] suggest the possibility that some cases represent unrecognized cholelithiasis with passage of stones. These special cases are infre-

quent and do not constitute a practical limitation to the use of needle biopsy. Since the biopsy diagnosis of hepatitis is readily made early in the disease,[99, 107] when the changes caused by obstructive jaundice are minimal, it appears desirable to perform liver biopsy relatively early in doubtful cases. Although the lesions of unrelieved obstructive jaundice become more pronounced with the passage of time,[99, 107] the differentiation from hepatic jaundice may become more difficult because the characteristic parenchymal changes of the latter may no longer be manifest and the portal changes may then closely resemble those of extrahepatic biliary obstruction.[5, 18, 99, 107] The use of repeat biopsy may resolve cases not clarified by initial biopsy.

Because of the recognized danger of needle biopsy in the presence of obstructive jaundice, however, its use should be limited to cases not otherwise resolvable, as pointed out in the concluding section under the discussion of complications. In practice, this means that the clinical and laboratory work-up of the patient with jaundice must be made promptly so that early decision concerning the use of needle biopsy can be made at a time when it will be most helpful. All too frequently patients with jaundice are followed for unduly protracted periods. The information gained by biopsy may then be less useful.

Disease of the biliary tract, including common-duct stones, is notoriously deceptive clinically and is frequently overlooked in older patients. The first attack may subside spontaneously and be misdiagnosed as hepatitis. Only appropriate therapy, however, may spare the patient subsequent attacks and the ensuing complications. Patients with previously undiagnosed common-duct stones are often seen after irreversible liver damage has occurred, and little can be done. A survey of 6062 consecutive autopsies performed between 1945 and 1951 at the Mallory Institute of Pathology disclosed 46 patients with complete or partial obstruction of the common duct by stones, most of which were unsuspected before autopsy.[113] In almost 80 per cent of these cases the biliary-tract disease or its complications were the primary or contributing cause of death. Of the 20,016 biopsies reviewed in this study, on the other hand, only 6 deaths appeared clearly related to biopsy in patients with obstructive jaundice. Needle biopsy of the liver has been repeatedly performed in patients with obstructive jaundice without serious complication.[8, 9, 13, 21, 24, 25, 104, 107] There is general agreement that the usefulness of the procedure far outweighs its potential risk.

Detection of Neoplasms of the Liver

It is almost impossible to make an accurate[21, 114] early clinical diagnosis of cancer of the liver, primary or metastatic. It is well known that a large portion of the organ may be replaced by tumor without jaundice or laboratory abnormality. In older persons, an erroneous diagnosis of liver neoplasm is often made when hepatomegaly is found. The hazard of ascribing malignant attributes to so-called "palpable" nodules of the liver is well known. Equally unreliable is the diagnosis of cancer based merely on the hard consistence of nodules clearly felt. Needle biopsy has proved to be particularly useful in the diagnosis of this condition, and almost all reports agree that the majority of such lesions are successfully needled.[1, 18, 19, 22, 46, 107] Of 53 patients with malignant liver neoplasms, biopsy showed cancer in 41 (77 per cent), and in 5 of the remainder failure to obtain tissue was responsible.[115] After initial failure repeated biopsy established the diagnosis in several cases. Schiff[18] reported that the diagnosis of metastatic carcinoma was made on clinical grounds in 16 patients who were shown by subsequent biopsy to have non-neoplastic lesions, including obstructive jaundice (3 patients), fatty liver (2 patients) and hepatitis (1 patient). Clinical diagnosis of carcinoma of the liver, primary or metastatic, should not be accepted without convincing confirmatory evidence. Liver biopsy provides the only simple means for accomplishing this.

The demonstration of malignant tissue in the liver of a patient with known or suspected primary neoplasm elsewhere may save the patient an unnecessary exploratory laparotomy. When neoplastic tissue is not obtained in suspected cases of liver neoplasm it may be desirable to take a biopsy later at other sites.[20, 115] Immediate repetition of the biopsy may be considered if the tissue obtained does not present typical gross features of neoplasia.

Evaluation of Therapy and Prognosis in Cases of Known Liver Disease

Volwiler and Jones,[13, 38, 43] Schiff[18] and others[40, 41, 102, 116] used needle biopsy in evaluating the course of patients with fatty liver,[42, 68, 70, 81, 117] cirrhosis and infectious hepatitis.[9, 20, 26, 78, 118, 119] Studies from the Boston City Hospital have shown that in the fatty liver of acute alcoholism apparent clinical and functional liver improvement sometimes exists without corresponding diminution of liver fat.[20] Thus, patients with markedly fatty liver, fed diets free of protein, showed return of appetite, loss of jaundice, diminution in size of liver and loss of tenderness as well as improvement of liver function. Marked reduction in liver fat did not occur until a liberal diet containing adequate amounts of all nutrients including protein had been provided. It is not possible on the basis of clinical or functional tests alone to determine when the liver has become free of fat or when all evidence of activity of hepatitis has disappeared. Despite apparent similarity of clinical course and treatment, one patient with Laënnec's cirrhosis may remain stabilized without progressive disability, whereas another may show a marked increase in fibrosis with attendant complications. Follow-up biopsies provide the only means

of recognizing early the differing prognoses in such cases. Correct diagnosis permits application of specific therapy in diseases such as tuberculosis, brucellosis, parasitic infestation, Weil's disease, hemochromatosis, fungous disease and amebiasis. Contrariwise, unwarranted therapy, hazardous to an already damaged liver may be avoided.[120, 121]

Thus, Himsworth[122] considers the biopsy an aid to therapy:

> Owing to the great functional reserves of the liver, apparent clinical recovery from infective hepatitis may have occurred at a time when the organ is still the seat of pathological changes. Experience has shown that a careless regime of life may lead to an exacerbation of illness in such cases. It is difficult to convey to a patient imbued with the sense of returning well being the conviction that continued precautions are still necessary unless the doctor himself is inspired by the certainty of his diagnosis. In fibrotic conditions of the liver an exact diagnosis can be a decisive factor in prolonging the patient's life. Little can be done for cases of post-necrotic scarring, but much for the diffuse hepatic fibroses following fatty infiltration. The discovery of fat-laden parenchymal cells in a liver diffusely fibrotic to a great or less degree, is an indication that the liver cells are malnourished and in urgent need of substances which can be supplied by appropriate dietetic therapy. The majority of such cases in temperate climates are alcoholics, who are notoriously unsatisfactory patients. Their survival may often depend upon the insistence with which they are pressed to reform their vicious habits, and adhere to an appropriate dietary. The seriousness of such cases is often not clinically obvious until their last stages. Puncture biopsy by allowing its appreciation at an earlier stage may enable a decisive influence to be brought to bear on many members of this group while their illness is still curable. These are all practical considerations directly related to the patient's welfare in particular cases. . . .

Liver Biopsy in Splenic-Vein and Portal-Vein Surgery

Linton[123] has pointed out that the type of shunting operation employed for the relief of portal hypertension depends on the location of the portal block, portacaval anastomosis being the procedure of choice in intrahepatic block and splenorenal anastomosis in extrahepatic types. Accordingly, Schiff[18] used liver biopsy to help distinguish between these lesions in cases scheduled for surgery. In the Post-Graduate Hospital in London liver biopsy was routinely performed before splenectomy was carried out. Sherlock believed that many patients with leukemia, myelosclerosis or hemochromatosis were spared unwarranted splenectomy by this procedure.[124] Similarly, at the Mayo Clinic, liver biopsies were performed on patients with thrombocytopenia to differentiate the idiopathic variety, for which splenectomy is indicated, and the type secondary to hepatosplenomegaly, for which it may be contraindicated.[125] These authors stated that the procedure of liver biopsy could be done with "negligible risk" even in the presence of clinical purpura.

Liver Biopsy in Evaluation of Disability

Kahn et al.[126] and Sulkin and Pike[127] suggested that viral hepatitis may be an occupational disease of laboratory personnel who handle blood and blood products. Dishwashers are particularly prone to infection through superficial cuts from contaminated glassware. Brucellosis, Weil's disease and hepatoses secondary to toxic chemicals such as carbon tetrachloride and other halogenated hydrocarbons are also industrial problems. The difficulty of determining compensation for disability derives in part from the uncertain initial diagnosis (especially in the absence of jaundice) and the nonspecific nature and variable duration of the symptoms. A similar problem has resulted from the large number of cases of epidemic and serum hepatitis in the armed forces. Positive biopsy information can help to clarify doubtful cases.

Liver Biopsy in Diagnosis and Treatment of Liver Abscess

Van Raalte[100] stated that when the possibility of a large amebic abscess of the liver exists, exploratory needle biopsy through the posterior axillary line just below the diaphragm was the method of choice for both diagnosis and treatment, pointing out that Ochsner and DeBakey[128] found a 5.6 per cent mortality in the closed method of drainage as compared with 43.1 in abdominal exploration with open drainage.

Liver Biopsy in Pregnancy

Both the recognition of liver disease and the differential diagnosis of the cause of jaundice are especially difficult in pregnancy because of the frequent occurrence in normal pregnancy of digestive symptoms, vascular spiders and palmar erythema, as well as impaired liver-function tests. The special disorders of the liver associated with pregnancy and its complications such as "jaundice of pregnancy," hyperemesis gravidarum and eclampsia must be added to the list of liver disorders.[129] Martin and Ferguson,[130] differing from Zondek and Bromberg,[131] stated that interruption of the pregnancy should be considered in cases of severe hepatitis. Nixon et al.[132] and Ingerslev and Teilum[133] performed needle biopsy of the liver on normal pregnant women and on women with pre-eclamptic toxemia, eclampsia and infectious hepatitis without complication. Nixon and his co-workers believed that the decision for therapeutic abortion could be made in certain cases of severe hepatitis or acute atrophy on the basis of biopsy findings. Morphologically mild infectious hepatitis alone did not warrant this procedure. Ingerslev and Teilum demonstrated the histologic identity of the liver of the normal pregnant and nonpregnant woman.

Liver Biopsy in Children

Keller and Nute[134] and Harrell and McBryde[135] reviewed the occurrence of cirrhosis of the liver in children. Since untreated obstructive biliary cirrhosis may progress to death at an early age, the former authors recommended the use of liver biopsy at laparotomy for early diagnosis. Gillman and Gillman[4, 136] performed 181 needle biopsies without mishap on children with infantile pellagra. This group included 37 biopsies on children aged three to twelve

years, 72 on children aged thirteen months to two years and 72 on infants one year or less. As many as four biopsies were performed on several children, including 1 aged six months. These authors considered the procedure indispensable for establishing diagnosis and for assessing the effectiveness of any form of therapy. Meneghello and his associates[137] performed 89 biopsies on 29 children in the course of a year without accident and with only 3 failures to obtain liver tissue. In this country needle biopsy of the liver has not yet been generally accepted as a routine diagnostic procedure in children. Owing to lack of co-operation on the part of children, Gellis[138] prefers surgical biopsy. He reserves needle biopsy for children who cannot tolerate even short-lasting anesthesia. He reports no deaths in a small series performed on infants and children.

Liver Biopsy as an Investigative Tool

More than any other single method liver biopsy has contributed to the present understanding of the pathogenesis of clinical liver disease.[7, 80, 94, 139-141] The inspection of routine microscopical slides alone has helped elucidate the course of hepatitis,[3, 8, 29, 36, 38, 61, 142, 143] fatty liver,[38-42, 144] the cirrhoses (portal,[43, 116, 117, 142, 145-147] cardiac,[27, 148] biliary[110] and atrophic[142, 149]), obstructive jaundice,[106, 107] infectious mononucleosis,[64, 99] Wilson's disease,[86-88] von Gierke's disease,[150] sarcoidosis,[97, 98] brucellosis,[35, 36] tuberculosis[96] and pellagra.[151] Today, there are available a variety of newer technics, largely histochemical, which selectively stain chemical substances within individual cells.[152, 153] Nucleic acids, for example, may be selectively stained by basic dyes such as methylene blue[154, 155] and methyl green pyronine.[156] Since a relation between nucleic acids and intracellular protein synthesis has been demonstrated,[157] these dyes may be used to assay protein synthesis in the liver cell.[158] Newer methods allow the staining and classification of proteins according to their affinity for acid and basic dyes[159] and according to their content of reactive sulfhydryl[159] and amino[160] groups.

Liver glycogen is best identified by staining with Schiff's leukofuchsin reagent after oxidation with periodic acid.[155] A uniform intracellular distribution of glycogen obtains when the liver sample is fixed in cold alcohol-formol-acetic acid.[161] By the use of saliva digestion before staining with the periodic-acid-Schiff technic, alcohol-insoluble carbohydrate complexes can be readily distinguished from glycogen.[162] Study of the role of the human liver in carbohydrate metabolism has been aided by this method.[163-166] The amount and distribution of liver glycogen vary widely in liver disease.[167, 168] Among the many interesting and unexplained findings is the occurrence of glycogen within the nuclei of liver cells in many cases of diabetes mellitus.[169]

The staining of lipids with Sudan dyes constitutes the most precise histochemical test now available.[170] Sudan black B is preferred because of its dense color and wide affinity for almost all types of lipids, including bound cytoplasmic lipids as well as the neutral fats of the liver cell.[170] Histochemical studies have altered the concept of the significance of lipid accumulation in the liver. The large empty spaces seen in conventional paraffin sections of fatty livers are often taken as evidence of severely impaired functional capacity. Histochemical examination, however, shows that even these fat-filled cells are rimmed by cytoplasm containing abundant glycogen, some pentose nucleic acid and a healthy looking mitochondrial apparatus.[171, 172] The Baker acid hematin test is specific for phospholipids.[173] It gives a picture in liver biopsies similar if not identical to that produced by one of the classic mitochondrial technics.[17] Mitochondria, which contain the cellular respiratory enzymes, are altered in liver disease and are of special significance in fatty liver.[171] Additional lipids are demonstrable with carbonyl reagents in the cytoplasm of liver cells.[174] The distribution of vitamin A in the liver has been studied by means of fluorescence microscopy.[175]

A variety of enzymes can be localized by staining reactions[152, 176] including acid and alkaline phosphatase,[177-180] esterases,[181] succinic dehyrogenase,[182] sulfatase, beta-glucuronidase and others.[183] For these reactions tissues are best frozen rapidly and sectioned in a cryostat.[185] Needle biopsy makes available living human tissue for study by these and other physical and biochemical technics such as tissue culture,[186] microrespirometry,[188, 189] microchemistry,[187-190] isotopic[191] and radioaudographic[192] procedures and electron microscopy.[193] More complete understanding of the normal and diseased liver can be expected in the coming years as these methods are applied more widely.[139]

(To be concluded)

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MEDICAL INTELLIGENCE

DEATH FOLLOWING ANGIOCARDIOGRAPHY*

Report of Two Cases after Administration of Diodrast and Neo-Iopax, Respectively

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AMONG 6824 cases collected by Dotter and Jackson§ from 182 hospitals, in which angiocardiography had been used as a diagnostic procedure, deaths occurred in 26 cases, or 0.38 per cent. In 25 Diodrast, Diodone or Pyelosil was used. We have been unable to find a report of death after injection of Neo-Iopax for angiocardiography. One death during an arteriogram, not an angiocardiogram, with Neo-Iopax as the contrast substance, has been reported.§

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§Dotter, C. T., and Jackson, P. S. Death following angiocardiography *Radiology* 56:527-533, 1950.

In the following cases death was due to angiocardiography, Diodrast being given in 1 and Neo-Iopax in the other (Table 1).

CASE 1. J. O., a 43-year-old woman, was admitted to the hospital on April 16, 1952, with a chief complaint of blueness, shortness of breath and swollen ankles for 2½ years. There had been questionable cyanosis at birth, and play had been limited because of dyspnea in childhood. The patient had 11 sisters and brothers, all alive and well.

Physical examination revealed a well developed, chronically ill woman with cyanosis of the lips, fingers and toes. The head and neck were normal, and the lungs were clear. Auscultation of the heart demonstrated a harsh systolic murmur at the 2d interspace at the left sternal border. At the apex a systolic murmur and a late diastolic crescendo murmur could be heard. There was a systolic thrill over the left precordium. The apex was in the 5th interspace and at the anterior axillary line. The abdomen was distended, and the liver edge was palpable 1 fingerbreadth below the right costal margin. There was moderate clubbing of the fingers and toes.

The blood pressure was 130/90. The pulse was 80 and regular, and the respirations 24.

The urine gave a + test for albumin but was otherwise normal. Examination of the blood showed a red-cell count of 5,180,000 with a hemoglobin of 101 per cent, and a white-cell count of 7000, with a normal differential. A serologic test for syphilis was negative. The nonprotein nitrogen was 39 mg., and the creatinine 1.6 mg. per 100 cc.; blood sugar and serum sodium, potassium, chloride and carbon dioxide combining power were normal. Liver-function tests were negative.

An electrocardiogram disclosed right-bundle-branch block.

Fluoroscopic examination revealed generalized cardiac enlargement, with marked bulging and forceful pulsation of the pulmonary outflow tract. The right and left pulmonary arteries presented prominent shadows; hilar markings were greatly exaggerated and pulsatile. Barium-swallow examination indicated marked posterior displacement of the esophagus. The lung fields were clear.

Preparatory medication consisted of 0.4 gm. of quinidine, 5 hours and 2 hours before the procedure, and 100 mg. of cortisone and 0.2 gm. of Seconal 2 hours before angiocardiography.

A skin sensitivity test was negative; 60 cc. of 70 per cent concentrated Diodrast was injected intravenously, and 6 films were

taken over a period of 15 seconds. The patient gasped immediately after the dye was given, became cyanotic and complained of a warm sensation and headache. Oxygen under pressure and artificial respiration were immediately begun. No heart sounds could be heard. Coramine was given. Artificial respiration was continued for 30 minutes, but the patient did not again respond.

At autopsy the pulmonary veins from the right lung were found to empty into the right atrium; the foramen ovale was widely patent. There were also chronic stenosis of the mitral valve, severe right-sided hypertrophy and chronic passive congestion of the various organs.

TABLE 1. *Data in 2 Cases of Sudden Death after Angiocardiography.*

Case No.	Preparatory Medication	Contrast Medium			Skin Test for Sensitivity	Effect of Angiocardiography	Autopsy Findings
		Drug	Amount	Strength			
			cc.	%			
1	Quinidine (0.4 gm.) 5 & 2 hr., cortisone (100 mg.) 5 hr. & Seconal (0.2 gm.) 2 hr. before angiocardiography	Diodrast	60	70	Negative	Immediately after injection warm sensation, headache & arrhythmia with some coupled beats, followed in 30 min. by respiratory arrest; coramine by intravenous injection, oxygen & artificial respiration without effect.	Pulmonary veins on right entering right atrium; widely patent foramen ovale; stenosis of mitral valve.
2	Quinidine (0.2 gm.) & Nembutal (0.1 gm.) 3 hr. before angiocardiography	Neo-Iopax	27	75	Negative	Cardiac arrest 45 sec. after injection; normal rhythm restored after intracardiac instillation of epinephrine; few min. later ventricular fibrillation occurred; Pronestyl, cardiac massage & electric defibrillation without effect; patient died 3 hr. later.	Primary proliferative pulmonary arterial & arteriolar sclerosis

Special precautions were taken with all subsequent angiocardiograms. Not only was an anesthetist present but also endotracheal equipment and a thoracotomy tray were available. An electrocardiogram was recorded throughout each angiocardiogram. A tray with all the drugs for use in a cardiac emergency was in the room. Succeeding angiocardiographies were relatively uneventful until September 25, 1952, when a second death occurred.

CASE 2. G. C., a 9-year-old boy, reported that about 1 year before admission, while running to catch a bus, he had become pale and dyspneic and had been forced to stop and rest. After this he had several attacks at school on exertion. Easy fatigability and dyspnea developed progressively over the next 4 or 5 months and he was admitted to the hospital on September 25, 1952.

There was a history of "asthma" from 18 months of age, but the patient had been free from attacks the previous year and a half. There was no history of cyanosis. He was a full-term baby with a normal delivery and had 3 siblings, all alive and well.

Physical examination showed the left anterior aspect of the chest to be slightly prominent. A Grade 1 systolic murmur was heard over the base and along the left sternal border in the 3d intercostal space. The aortic 2d sound was equal to the pulmonic. The lungs were clear; the liver was not enlarged. There was no clubbing of the fingers and toes and no cyanosis or edema. Peripheral pulses were normal.

The pulse was 100. The blood pressure was 100/65.

Urinalysis was negative. Examination of the blood revealed a red-cell count of 4,770,000, with a hemoglobin of 95 per cent, and a white-cell count of 10,600, with 42 per cent neutrophils, 45 per cent lymphocytes, 5 per cent eosinophils and 8 per cent monocytes.

An electrocardiogram demonstrated slight peaking of the P waves, with the pattern of hypertrophy and strain of the right ventricle.

Fluoroscopic examination disclosed a pulmonary conus, with active pulsations.

On the 2d hospital day cardiac catheterization revealed an increase in the wedge pressure (15 mm. of mercury), and in pressure in the pulmonary artery (105/65), right ventricle (105/0) and right atrium (mean of 7 mm. of mercury). The oxygen content of 10.7 vol. per cent (59.6 per cent saturation) was identical in all the right-side heart chambers. About 30 minutes after the catheterization, angiocardiography was done by injection of Neo-Iopax 1 cc. per kilogram of body weight, into the antecubital vein (premedication had consisted of 0.1 gm. of Nembutal and 2 gm. of quinidine). The skin test was negative. Forty-five seconds after injection of the Neo-Iopax the pulse suddenly became undetectable, and there were no audible heart sounds though on auscultation of the chest wheezes were heard. Immediately 1 cc. of 0.1 per cent epinephrine was injected into the heart and a normal heart beat restored, persisting for several minutes. Oxygen, by mask, was given from the moment of injection of the dye. Cardiac arrest again ensued within 30 seconds; the chest was opened at once, and massage instituted. Electric defibrillation was attempted 3 times, but normal cardiac rhythm could not be restored. Pronestyl was given. Massage was continued for 3 hours, without effect.

FIGURE 1. *Samples of the Arrhythmia Recorded in Case 2, at Intervals of Approximately Five Minutes during the Period after Injection.*

A continuous record of the electric activity of the heart was made. Arrhythmias were noted, varying from auriculoventricular dissociation to ventricular tachycardia and then to ventricular fibrillation. The type of arrhythmia noted during the last 45 minutes, terminating with minimal twitching of the ventricular is shown in Figure 1.

Autopsy demonstrated primary proliferative pulmonary arterial and arteriolar sclerosis and chronic cor pulmonale, with hypertrophy and dilatation of the right ventricle, pulmonic and tricuspid valves and pulmonary artery. The pathological picture was that of pulmonary endarteritis.

Discussion

These 2 fatal cases, occurring in spite of what seemed to be adequate protective safety measures, have been cause for considerable inspection of the need for any given angiocardiogram at this institution. Our experience in more than 300 catheterizations of the right side of the heart without serious complications, but with 2 deaths in approximately 100 angiocardiograms, has resulted in our considering catheterization as the diagnostic procedure of choice. We appreciate that the two technics are not fully interchangeable, but should complement each other. In occasional cases this is true, but in most patients competent catheterization, done by experienced observers, can supply precise, definitive information that is not subject to the vagaries of interpretation associated with the shadows of dye.

The advantages of angiocardiography are in the speed of the test; no complicated manipulation or protracted laboratory work is necessary. However, in our opinion, the risk to the patient's life that is brought into play the instant the dye is thrust into the blood stream must be justified by an imperative need for diagnostic information; the information must have value in terms of the patient's welfare — value that offsets the risk to his life.

Summary

Two deaths associated with angiocardiography are reported. The first patient died immediately after the injection of 60 cc. of 70 per cent Diodrast. Autopsy demonstrated aberrant pulmonary veins, patent foramen ovale and stenosis of the mitral valve. The second patient died immediately after the injection of 27 cc. of 75 per cent Neo-Iopax. Autopsy demonstrated primary proliferative pulmonary arterial and arteriolar sclerosis.

LATE ULCERATION TWENTY YEARS AFTER IMPLANTATION OF RADON SEEDS

Report of a Case

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RADON, a noble gas and an immediate descendant of the metallic element, radium, finds great practical use in the interstitial radiotherapy of malignant tumors of the body. Like radium, radon in itself has little value, for it emits only alpha rays. However, its immediate decay products, radium B and radium C, emit beta and gamma rays, the therapeutically effective radiations.

Radon gas is collected from a water solution of a soluble radium salt, purified and concentrated in tiny hermetically sealed containers of fine gold tubing. The radon seeds in present use are about 4 mm. long, with a wall thickness of 0.3 mm. and an external diameter of 0.75 mm. When first prepared they contain about 0.5 to 4 mc. of radon (a mc. is the quantity of radon in equilibrium with 1 gm. of radium[1]).

Because of their small size radon seeds are implanted with much less trauma to tissue than the usual radium needles, which must also be removed from the tissue, with more trauma, whereas the radon seeds are frequently left in situ permanently with no ill effects. If the seeds are placed too near the surface, or if there is considerable necrosis and ulceration in the tumor itself, they occasionally slough out spontaneously. Radon has a half-life of 3.85 days, losing 15 per cent of its value a day, with an average life of 132 days. However, within a week of its collection and insertion into the body the radiation is so feeble that it has no effect on the surrounding tissue.[2]

The following case is of interest in that fifteen years after their insertion 2 of 4 radon seeds spontaneously sloughed out of a healed area of the skin.

A. L. M., a 45-year-old school teacher, was first seen by one of us (J. G. D.) in August, 1933. At that time she presented a nodular, indurated, pearly-bordered, tumor of the chin, 1 cm. wide, of 2 years' duration. Clinically, it was a typical basal-cell epithelioma. The entire lesion and a zone of normal-appearing skin about it were electrodesiccated and curetted deeply and vigorously. Three weeks later the area was treated with radium. The lesion remained well except for occasional small border nodules, which were electrodesiccated. In October, 1936, the growth recurred, and on October 8, 4 radon seeds were inserted into the lesion. The patient was examined periodically for 3 years, with no evidence of recurrence of the tumor. On February 27, 1953, she had a sharp pain and swelling and redness in this area. On March 16 the area ulcerated, and she noticed a small

Figure 1. *Ulceration from Radon Seeds.*

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gold metal extending from the ulcer. When she pressed the area another one appeared; both were removed by the patient. When she was examined on March 31 there was an ulcer, 1 cm. in diameter, with considerable edema and erythema (Fig. 1). There was no evidence of any malignant degeneration. Under suitable therapy the ulcer healed rapidly. Roentgenologic examination of the jaw revealed the presence of 2 small, cylindrical, metallic objects in the soft tissues anterior to the mandible (Fig. 1). One was deeply placed and parallel to the surface of the overlying skin; the other was more superficially located and perpendicular to the surface of the skin.

It was our impression that the constant motion of the tissues overlying the bony area had gradually forced the two radon seeds nearer and nearer to the surface. Only when these metallic bodies approached and penetrated the cutis and epidermis was a foreign-body reaction elicited, with resultant inflammation, ulceration and final extrusion of the gold seeds. The radon seed deeply situated in the subcutaneous tissues will probably cause no trouble, but the other, more superficially located, may duplicate the behavior of its two extruded fellows at some time in the near future.

Summary

A brief discussion of the nature, preparation and use of radon seeds is presented. A case in which two of four radon seeds implanted sixteen years previously produced a severe but short-lived foreign-body reaction in a healed scar, the site of a clinically cured basal-cell epithelioma, is reported.

Figure 2. *X-ray Film, Showing the Two Radon Seeds Still Present in the Tissue.*

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CASE 39511

PRESENTATION OF CASE

A forty-six-year-old man was referred to the hospital because of bilaterally enlarged, tender breasts.

Two years before admission, when he was seen at another hospital with the same complaint, he gave a history of enlarged breasts since puberty that had become tender only during the previous two months. He had gained 10 pounds during the three months before admission. He had been married for eighteen years and had had satisfactory sexual relations with his wife although they had never had any children despite the fact that contraceptive measures were not used. In the past he had been able to sing, but during the last twenty years he had been unable to do so because of hoarseness. He admitted to having a moderate alcoholic intake. Physical examination showed a well developed and well nourished man with a good layer of adipose tissue of questionable female distribution. The hips were wide in comparison to the chest. Axillary and pubic hair and the genitals were considered to be normal. The breasts were large and firm, and tender about the areolae. The rest of the examination was negative, as were routine blood and urine studies. The blood sugar was 97 mg. per 100 cc.; the basal metabolic rate −8.8 per cent. A roentgenogram of the sella turcica was normal. The patient did not return to the other hospital for recommended studies; however, it was learned that the tenderness of the breasts had disappeared. He was next seen two years later on return of this symptom, when he admitted to having lost interest in sexual relations. Positive physical findings included soft skin, sparse facial hair and a small thyroid cartilage. There was temporal recession of the hairline; growth and distribution of axillary and pubic hair were normal; there was no hair on the chest and abdomen. The breasts were enlarged, and the left was rather tender. The testicles were half the normal size. He denied ever having had mumps, orchitis, syphilis or penile lesions. Routine examination of the blood was normal. Thymol turbidity and bromsulfalein retention were normal; blood Hinton and Wassermann tests were negative.

On admission the history and physical findings were confirmed.

Laboratory studies included 17-ketosteroids of 8.2 mg. per twenty-four hours and FSH (follicle-stimulating hormone) weakly positive for 104 mouse units per 24 hours when assayed by the method assuming too little excretion in the urine, and positive for 192 and negative for 384 mouse units per twenty-four hours when assayed by the method assuming too much excretion (normal, 6.5 to 26 mouse units).

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JACOB LERMAN*: This short protocol does not provide much data for discussion. I was puzzled why an operation was done. All sorts of procedures are called operations. This "operation" may have been a biopsy or a major surgical procedure. A major operation on this type of patient would mean the removal of some tumor. At the outset, I should say I do not believe he had a tumor because none was found on physical examination, but for the purpose of discussion I shall assume that a tumor was missed and that the surgeons were looking for it.

What kind of tumors can produce gynecomastia? One has to consider three sources in such a patient — the pituitary and adrenal glands and the testes. A tumor of the pituitary gland can produce gynecomastia, but usually there is evidence of pressure phenomena in the head and changes in the sella turcica are visualized in the x-ray films; it would be simple from x-ray changes and associated symptoms to make that diagnosis. A small adenoma could produce the symptom of gynecomastia and feminization, perhaps without causing pressure phenomena in the head. Under such conditions there would be stimulation of the breast by the lactogenic hormone and also stimulation of the other glands to produce a high urinary excretion of the 17-ketosteroids. Since the 17-ketosteroids were low normal I can assume that a tumor of the pituitary gland was not causing the changes in the breast.

Adrenal tumors occasionally produce estrogens as well as other hormones and thus can result in gynecomastia and evidence of hypogonadism. Here, also, the predominant stimulus is the production of 17-ketosteroids, which are very high. Because of the high estrogen production and perhaps of the high 17-ketosteroid production, FSH is usually low or normal. Again, there is no evidence chemically for a tumor of the adrenal gland and certainly no evidence by examination of a tumor in the abdomen.

The testis is the third source of tumors that give rise to gynecomastia. The testicular tumors are of

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various types — chorionepitheliomas, interstitial-cell tumors and seminomas; many are teratomatous in origin. The interstitial-cell tumors can cause gynecomastia and hypogonadism. As a rule they produce a large amount of 17-ketosteroids in the urine, and the FSH is usually low or normal. If this patient had a tumor of the testicle it would have been obvious because on two occasions the testicles were examined and found to be either normal or slightly smaller than normal. Consequently, on this basis alone I can eliminate the possibility of a tumor of the testicle.

Cirrhosis, among other causes of gynecomastia, undoubtedly was considered by the examiners. The patient had an alcoholic intake of abnormal proportions, but the examiners ruled out evidence of liver disease by the tests. On physical examination there was no evidence of a large liver or of jaundice to suggest that the liver played a role in the gynecomastia. In the cases in which the liver is diseased, the estrogens in the blood and urine are excessive and produce stimulation of the breasts, but also the FSH is usually low or normal because of the excessive amount of estrogens. We have seen gynecomastia with hyperthyroidism, particularly in younger patients. The gynecomastia is sometimes unilateral and sometimes bilateral, and sometimes affects first one breast and then the other. I think it would have been quite obvious if the patient had had hyperthyroidism.

The remaining cause of gynecomastia is a functional disturbance that we can label hypogonadism, as described by Klinefelter, Reifenstein and Albright.[1] In this syndrome the seminiferous tubules are damaged — fibrosed and hyalinized — and the interstitial cells (Leydig cells) are increased; there are hypogonadism associated with gynecomastia, a high FSH and normal or low ketosteroids. This patient had normal pubic and axillary hair and recession of the hairline of the male so that there was clinical evidence of persistence of androgen production by the Leydig cells. This entity is usually evident a few years after puberty and persists throughout life. There is normal sex life as a rule because the secondary sex characteristics are not affected too much. Since this is the presumptive diagnosis, I can assume that the patient had a biopsy of the testicle, and I expect it to have shown hyalinization of the seminiferous tubules with persistence of the Leydig cells in more or less normal condition.

It occurs to me that another type of operation may have been done: the patient may have been sent to the hospital for operation on the breasts. This is done when the patient has tender breasts or breasts that are unsightly. There is no specific treatment for gynecomastia.

I think that the diagnosis was quite clearly the so-called Klinefelter–Reifenstein–Albright syndrome and that the operation was a biopsy of the gonads.

Clinical Diagnosis

Klinefelter's syndrome.

Dr. Jacob Lerman's Diagnosis

Klinefelter–Reifenstein–Albright syndrome.

Anatomical Diagnosis

Klinefelter's syndrome.

Pathological Discussion

Dr. Ronald C. Sniffen: As Dr. Lerman predicted the operation was a testicular biopsy and microscopically was typical of the so-called Klinefelter syndrome. In this disease there is progressive sclerosis of the tubules, and in the case under discussion many of them had been converted into fibrous cords. Some of the tubules were lined only by Sertoli cells; in others, however, there were a few spermatogenic cells. One of the outstanding findings in the condition is hyperplasia of the interstitial cells, which may reach large proportions (Fig. 1).

Figure 1. *Photomicrograph of Testicular Biopsy, Showing Sclerosis of the Tubules and a Large Island of Leydig Cells.*

There is a great difference in the morphology of the Leydig cells from case to case. Sometimes they seem to be qualitatively normal, but often they are distinctly abnormal and are misshapen and ill defined and frequently resemble fibrocytes; histochemical methods may indicate a marked diminution in secretory activity. There is a nebulous correlation between the degree of eunuchoidism and the aberrations in the Leydig cells. Clinically the disease

apparently exists at puberty; the pathological findings bear out this impression, for immature tubules are often found among the sclerotic tubules. Therefore, there is both failure of tubular maturation and sclerosis.

At times these patients have marked gynecomastia. Microscopically, the breast shows an increase in collagenous stroma without apparent glandular stimulation. This differs from the gynecomastia produced by estrogen therapy, which results in glandular hyperplasia.

In hypogonadotrophic eunuchoidism with a low urinary excretion of pituitary gonadotrophins, either idiopathic or the result of an organic lesion occurring in the pituitary gland before puberty, the testes remain in a prepuberal condition, with immature tubules and no visible Leydig cells. The picture is therefore quite different from that seen in Klinefelter's syndrome. If these patients are treated with chorionic gonadotrophin, Leydig cells appear, and spermatogenesis develops. Hormonal therapy does not benefit the testis in Klinefelter's syndrome.

In myotonic dystrophy, a polyglandular familial disease in which testicular atrophy occurs, the picture closely resembles Klinefelter's syndrome with tubular sclerosis and Leydig-cell hyperplasia. It is believed that the hormonal and somatic changes that take place in Klinefelter's syndrome result from primary disease in the testes, and judging from our 1 autopsied case[2] and reports in the European literature of the past the condition is associated with an increase in sparsely granulated basophils of the pituitary gland and a significant increase in the incidence of multinodular goiter and adrenal adenoma. The disease appears to be another anatomic demonstration of the interaction between the pituitary, thyroid and adrenal glands and the gonads.

DR. LERMAN: Is there any correlation between the amount of 17-ketosteroid excretion and the degree of hyperplasia of the Leydig cells?

DR. SNIFFEN: No; that has not worked out.

DR. FRED A. SIMMONS: I should like to take this opportunity to point out that we have now over 700 cases of testicular biopsies before and after all types of hormonal therapy on patients sixteen months to eighty-three years of age. The incidence of complication is extremely small. Three patients were rehospitalized for bleeding, which was easily controlled on the second admission. I should define it as an operation and not merely a biopsy, Dr. Lerman. However, it can be done almost on an outpatient basis. The patients come in on a Saturday morning without their breakfasts, are given Pentothal and leave at 4:00 p.m.; therefore, they do not lose time from work.

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CASE 39512

PRESENTATION OF CASE

First admission. A fifty-five-year-old housewife was admitted to the hospital because of increase in weight, weakness and ankle edema.

The patient dated her illness to a severe "cold" one year before admission, which was accompanied by copious sputum and coughing. The coughing persisted for several months but then left. She denied chills, fever, jaundice and change in the color of the urine with that illness. Six months later there was gradual loss of appetite and the onset of nausea that led to occasional vomiting four months before admission. She was studied at another hospital, where a diagnosis of cardiac cirrhosis with aortic stenosis was made. The findings at that time included hepatosplenomegaly, cyanosis, cough and mild jaundice. No ascites or hemangiomas were noted. The heart was said to have been enlarged to both sides, and the lung markings increased. A Graham test, gastrointestinal series and intravenous pyelogram were negative. Blood studies on that admission showed a nonprotein nitrogen of 35 mg., alkaline phosphatase of 1.3 Bodansky units, total protein of 7.0 gm., albumin of 2.45 gm. and globulin of 4.47 gm. per 100 cc. The icteric index was 22 units; the prothrombin time was 63 per cent, and cephalin flocculation was ++ in forty-eight hours. The hematocrit was 48 per cent, and the white-cell count 5100. The urine had a negative bile test with urobilinogen in a 1:500 dilution; the sediment contained 20 to 30 white cells per high-power field. The patient improved on a regimen of digitalis, vitamins and salt restriction. She felt better during the next four months until a week before admission, when she again noted nausea, vomiting, anorexia and fatigue. All medications were stopped, and she was referred to this hospital.

The past history included a cesarean section twenty-three years and an uneventful menopause fourteen years before admission. There was no history of rheumatic fever or previous jaundice. For six years she had worked in a shoe factory, where she was exposed to lacquers, thinners and dyes but she had not worked during the past five years. On repeated questioning she admitted taking a highball on rare social occasions.

Physical examination showed a moderately poorly nourished, generally icteric and slightly tanned woman. There were typical spider hemangiomas on the arms, face and upper back and ecchymoses on the thighs. The neck veins were collapsed when the patient sat at an angle of 40°; there was no hepatojugular reflex. The thyroid gland was not palpable, and both leaves of the diaphragm were high, with a few rales at the right lung base. The maximal cardiac impulse was in the fourth intercostal space 11 cm. to the left of the midsternal line. A systolic impulse was present in the second intercostal space

at the left of the sternum. The first mitral sound was loud, with a third sound heard in diastole at the apex. The aortic second sound equaled the pulmonic. There was a Grade 2 to 3 scratchy, harsh systolic murmur in the third intercostal space to the left of the sternum and a short blowing Grade 1 systolic murmur at the apex. The rhythm was sinus except for twelve to fifteen premature ventricular beats per minute. The abdomen was distended with fluid. The liver edge was palpable 15 cm. below the right costal margin and 12 cm. below the xiphoid process; the upper border was percussed to the fourth intercostal space. Although there was no ankle edema a + pitting edema of the sacrum was present. Neurologic examination was negative.

The temperature was 100°F., the pulse 130, and the respirations 20. The blood pressure was 148 systolic, 52 diastolic.

The urine was brown, had a pH of 5.5 and a specific gravity of 1.015 and gave a negative test for sugar and albumin and a + to +++ test for bile; the sediment contained 20 to 30 white cells in clumps per high-power field. Examination of the blood disclosed a hemoglobin of 11.5 gm. per 100 cc., a white-cell count of 7300, with a normal differential, and normal red cells. The total protein was 7.1 gm., the albumin 2.4 gm., the globulin 4.7 gm., the thymol turbidity 10.4 units (thymol flocculation ++++), the alkaline phosphatase 4.6 Bodansky units, the fasting blood sugar 124 mg., and the bilirubin 5.4 mg. total and 3.5 mg. direct per 100 cc. The prothrombin time was 37 per cent. The electrolytes were normal, and the blood Hinton test was negative. The stools were initially +++ to ++++ guaiac positive and became negative on the fourth day. An electrocardiogram demonstrated occasional ventricular premature beats, a normal axis and voltage, a normal sinus rhythm at a rate of 100, a PR interval of 0.20 second and a QRS interval of 0.08 second. The T waves were low in Leads 1, aVL, aVF, V_4 and V_5 and diphasic in Lead V_6; the ST segment was slightly sagging in Lead V_6. A chest film revealed elevation of both leaves of the diaphragm and a generally enlarged heart with a cardiothoracic ratio of 15.5:28. The trachea appeared deviated to the right. No varices were demonstrated on barium-swallow examination. A rounded density was seen at the upper pole of the right kidney.

The patient was treated with streptomycin, Hykinone and digitalis, with loss of some weight and clearing of the pyuria. Because of persistent mild tachycardia, thyroid-function studies were done and showed basal metabolic rates of +31, +30 and +28 per cent, protein bound iodide of 6.8 gamma per 100 cc. (normal, 4 to 8 gamma) and a radioactive iodide uptake of 33 per cent in forty-eight hours (normal, 25 to 50 per cent). The circulation time, arm-to-tongue method, was 8 seconds, and the venous pressure was equivalent to 60 to 70 mm. of saline solution. A diagnostic paracentesis was performed, and cytologic studies of the fluid were negative for tumor cells. On a high-calorie and low-salt diet she lost 5 pounds and felt much better. A therapeutic trial of potassium iodide brought no change and she was discharged a month after admission.

Final admission (six months later). She followed the recommended program well and felt better until the hot weather began three months before admission, when she noted fatigue, ankle swelling and anorexia. She gained 15 pounds in weight and was advised to re-enter the hospital.

Physical examination was unchanged except for the facts that the abdomen was greatly distended and tight, the skin was definitely icteric, the neck veins were slightly distended when the patient was raised to 40° and the spleen was felt 3 fingerbreadths below the left costal margin.

Laboratory studies were unchanged except for a bilirubin of 3.5 mg. per 100 cc. and guaiac-negative stools.

On the sixth hospital day she began to vomit first green and then red material that was guaiac positive, and had abdominal cramps. Because the hemoglobin was 10.5 gm. per 100 cc. she was given two blood transfusions. On the following day a flapping tremor of outstretched arms developed, and serial blood ammonia determinations showed a rise from 91 to 308 gamma per 100 cc. (normal 50 to 60 gamma) on the day of her death. Sodium glutamate, intravenous infusions of fructose and vitamin K were administered. She died quietly on the sixteenth hospital day.

Differential Diagnosis

Dr. Daniel S. Ellis*: It seems to me that the discussion in this case should attempt to determine the kind of heart disease and the kind of liver disease that this woman had. I think there can be no question that she had heart failure and liver failure, and I think death was due to a combination of the two.

Some questions were raised by the protocol that I do not think played any significant part in the course of this woman's illness or in her death. The clinicians were obviously concerned about some element of thyroid disease, but the only test that suggested increased thyroid activity was the elevated basal metabolic rate, which fits perfectly well with the degree of heart failure. The other tests of thyroid function were negative so I do not think on the basis of the evidence in the protocol that I have to consider hyperthyroidism as a part of the trouble. A deviation of the trachea was described and that may have been related to an enlarged thyroid gland. I wonder whether she had a substernal thyroid gland; if one was present I suspect it was probably incidental. Will Dr. Hanelin show the x-ray films?

Dr. Joseph Hanelin: The films made at the time of the first admission show an enlarged heart, with

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the left ventricle predominant, and moderate engorgement of the pulmonary vessels. The trachea does not appear to be deviated on these films. A barium-swallow examination was done on the first admission and again later. At neither examination were any varices shown. The first abdominal film shows massive ascites; it is difficult to differentiate the viscera although I suspect that the liver is down fairly low and the spleen may be enlarged although its outline cannot be traced well. The barium-enema examination is negative. A small calcification overlies the kidney; it may be a gallstone although I cannot rule out a renal calculus. In the films taken during the last admission, the ascites is again marked. There is more evidence of splenic enlargement, with the stomach displaced toward the midline, and of enlargement of the liver as indicated by the low position of the hepatic flexure.

DR. ELLIS: Do you have any evidence for a substernal thyroid goiter?

DR. HANELIN: No; I do not.

DR. ELLIS: Is there any widening of the esophagus that goes along with varices?

DR. HANELIN: No; I see no evidence of that.

DR. ELLIS: I think I shall dismiss as of no great importance any deviation of the trachea and the rounded density seen in the upper pole of the right kidney.

It seems that the so-called cold with copious sputum and coughing, to which the patient dated the onset of the illness, may have been the first bout of heart failure. The nausea and vomiting, which came next, would go perfectly well with passive congestion in the liver or any type of parenchymal liver disease. It is of interest that even at that time she had a marked disturbance in the protein content of the blood with an albumin of 2.5 gm. and a globulin of almost 5 gm. per 100 cc. She was jaundiced, and the cephalin flocculation of ++ is equivocal. I am given the information that she had been exposed to solvents, thinners and dyes, probably to raise the question of whether chemical damage to the liver played a part in the liver disease that obviously seems to have been present. This is a possible etiology.

Another point in the protocol is that she was slightly tanned; the protocol does not say what the time of year was, so I do not know whether the tan was from the sun or whether it is a clue to the fact that she may have had hemochromatosis. I shall simply note it and pass on. She did not have diabetes.

I shall first take up the question of the kind of heart disease she had. I should judge, from the auscultation of the heart, that she had murmurs that were consistent with an aortic stenosis and that the other murmurs present may have been due to a failing, perhaps dilated heart. I do not find anything that would make me certain that she had tricuspid-valve disease although I suspect that after some years of aortic-valve disease, left-sided heart failure having previously been present, right-sided heart failure may have developed, with dilatation of the valvular ring on the right side, causing considerable congestion in the portal circuit as well as in the systemic circuit. On the basis of the evidence I think she had aortic-valve disease with aortic stenosis, resulting in enlargement of the heart and heart failure.

What kind of liver disease did this patient have? She unquestionably had an advanced parenchymal liver disease that was growing worse during the time that this history followed her. The severe liver disease was manifested by jaundice, by the positive thymol flocculation, by the low albumin and high globulin, by the prothrombin time, which became increasingly long, by the anemia and terminally by signs of ammonia intoxication probably intensified by some bleeding. The extent of the hemorrhage during the last few days of the illness is not clear although it was recorded that she vomited blood, and after that she seems to have failed more rapidly. The last hemoglobin recorded was 10.5 gm. per 100 cc. For practical purposes, I should say that she had a form of cirrhosis.

There is no evidence of hepatitis or any other infection that might have played a part in the formation or development of the liver disease; therefore, I have no reason for implicating infection. She was known to take an occasional drink. What part alcohol played in the development of the cirrhosis or chronic hepatitis is not clear, but it does not seem to have been great. Nothing was said about her nutritional history. We believe that some nutritional lack is important in the development of cirrhosis. In the absence of any nutritional history I cannot say whether this applied to this patient.

I am left with two clues to the kind of cirrhosis this patient may have had; one is the history of heart failure, and the other is the suggestion that she had been exposed to chemical toxins, which may have damaged the liver. I could explain all this on the basis of chronic passive congestion and cardiac cirrhosis without implicating any other agent or type of liver disease. Because of the low serum albumin early in the history, however, I suspect that some process was present in the liver before the heart failure developed and that there may have been two elements in the liver disease. In the absence of any specific history of infection, alcoholism or nutritional lack, I shall say that she had cirrhosis due to chronic passive congestion as a result of heart failure and probably in addition toxic liver damage possibly caused by the chemical to which she had been exposed.

What caused the bleeding? At one time she had guaiac-positive stools and abdominal cramps. I

wonder whether along with the congestive heart failure she had a mesenteric thrombosis and guaiac-positive stools on that basis. That, of course, would not explain the vomiting of blood in the last illness. An infarction in the liver from thrombosis in the portal vein may have accounted for the final event. There was no x-ray evidence of varices although it is possible that she had them. She had a large, severely damaged liver and a large spleen, she bled terminally, and she had the picture of "ammonia intoxication" that frequently follows massive hemorrhage in patients with severe liver disease. Thus, I suggest that she had varices even though they could not be demonstrated.

My final diagnoses are aortic stenosis, cardiac hypertrophy and heart failure. Although I cannot rule out tricuspid disease, I think she did not have it. She had severe parenchymal liver disease — chronic passive congestion, cardiac cirrhosis and possibly also a portal type of cirrhosis. I suspect that she had esophageal varices.

DR. ALFRED KRANES: I am puzzled that Dr. Ellis placed so much emphasis on passive congestion. I do not see from the record what evidence there was for passive congestion. How could the patient have had such a large, congested liver from passive congestion with normal venous pressure, normal circulation time and all the rest?

DR. ELLIS: I remember several cases in which this question came up; the proof of the diagnosis seems to have been that when the heart failure was treated the liver grew smaller and the patient improved. At one time during the first admission this patient definitely improved, and the liver seemed to become smaller when the heart failure was treated.

DR. KRANES: It is only on the basis of treatment, then, that you make this diagnosis. Do you find anything in the record that would lead you to say that she had the congestion?

DR. ELLIS: She seems to have had pulmonary congestion at one time; she had dilated neck veins on the second admission.

DR. JOSEPH C. AUB: The electrocardiogram does not suggest that she had anything seriously wrong with the heart.

DR. MARIAN W. ROPES: I knew the patient only during her first admission. We were not impressed with any evidence of congestive heart failure and believed it would be unlikely that that played any prominent role in the liver disease. It was our impression that she had severe liver disease with cirrhosis, and we considered it more likely that it was slowly progressive chronic hepatitis, the factors for which were not evident.

DR. EDGAR B. TAFT: In the record, Dr. Ropes, you diagnosed high-output heart failure in this patient.

DR. ROPES: Our difficulty was that of deciding whether she had hyperthyroidism; we were not concerned about congestive heart failure, of which we thought she had relatively little. We were much impressed with the tachycardia and the high metabolic rate and were afraid we were missing a hyperthyroidism that might have been adversely affecting the liver disease so we studied her thoroughly. There were few corroborating laboratory findings. We did think we should follow through even to a therapeutic test. We finally concluded that the so-called high-output failure, which has been shown to be present in some cases of cirrhosis, explained the findings that we had first interpreted as those of hyperthyroidism.

DR. W. PETER U. JACKSON: The high basal metabolic rate, high pulse pressure and rapid circulation time would fit with the "high-output failure" described as occurring with severe liver disease by Paul Wood.*

DR. AUB: I am interested that Dr. Ropes was in charge of this patient and did not consider a generalized disease like amyloidosis, which I should think a good possibility.

DR. ROPES: I thought the degree of liver failure was greater than one would expect if amyloidosis played any major role.

A PHYSICIAN: Is it possible that the patient had a superimposed carcinoma of the liver?

DR. ELLIS: That possibility cannot be excluded, but nothing in the protocol makes me suspect that.

DR. AUB: May I add one word about the exposure to toxins? This patient was exposed to a great deal of carbon tetrachloride and possibly some benzene if she worked in a shoe factory some years before admission.

DR. ELLIS: This is important to know since patients who have been exposed to such solvents may have a transitory acute involvement of the liver at the time of exposure, with apparently a complete cure, and only later go on to develop a full-blown cirrhosis.

*Wood, P. *Diseases of the Heart and Circulation*. 589 pp. Philadelphia: Lippincott, 1950.

Clinical Diagnosis

Cirrhosis of liver, ? posthepatitis.
? Hepatoma.

Dr. Daniel S. Ellis' Diagnoses

Aortic stenosis.
Cardiac hypertrophy and failure.
Chronic passive congestion and cirrhosis of liver.

Anatomical Diagnoses

Hemochromatosis.
Splenomegaly.
Ascites and bilateral hydrothorax.

Pathological Discussion

Dr. Taft: At autopsy this patient still had ascites and some fluid in the pleural cavities as well. The heart was slightly enlarged, weighing 360 gm., but the coronary arteries and the valves were within normal limits for a person of her age. There was no evidence of the clinically suspected sclerosis of the aortic valve. There was only slight dilatation of the heart. There was also an anatomically patent foramen ovale, but this was functionally closed.

The main finding of pathological interest was the liver, which was markedly enlarged, weighed 1900 gm., and was described as a chocolate brown in the protocol. It was nodular, and the nodules were small. A piece of the liver treated with ferrocyanide and hydrochloric acid turned dark blue, showing that a large amount of hemosiderin was present in the liver parenchyma. The pancreas and adrenal gland, both cortex and medulla, were also quite brown and contained large amounts of hemosiderin. The thyroid gland was moderately small, weighing 8 gm., was firm and dark brown, and also contained much hemosiderin. The myocardium grossly was quite brown, but microscopically was not so impressively infiltrated with hemosiderin. In addition the hilar lymph nodes, the mucosa of the stomach, the kidneys, the pituitary and parathyroid glands and to a lesser extent the spleen and lungs were involved. We could not demonstrate iron pigmentation in the skin, although it was thought grossly to be there, nor was there any pigmentation in the ovary or esophagus. The spleen was quite large, weighing 650 gm., but no esophageal varices were demonstrated at autopsy.

Microscopical examination of the liver revealed marked fibrosis and a tremendous deposition of hemosiderin in the liver cells, fibrous tissue and epithelium of the ducts of the biliary radicles. Hemofuscin was also present. Although one does not hear so much about this pigment lately, when I trained at the Mallory Institute of Pathology a diagnosis of hemochromatosis was not made unless hemofuscin could be demonstrated histologically. Both Dr. Frank B. Mallory and Dr. Frederic Parker, Jr., considered that pigment the *sine qua non* of hemochromatosis; if there was no demonstrable hemofuscin, which is not an iron-containing pigment, they called such cases exogenous hemochromatosis or hemosiderosis.

One wonders why this patient had no diabetes since there was marked involvement of the pancreas by deposition of hemosiderin in both exocrine and endocrine portions. It is possible that the concomitant involvement of the adrenal and pituitary glands was sufficient to prevent the development of diabetes mellitus as a result of loss of function of islet tissue.

Dr. Hanelin: Was there a gallstone?

Dr. Taft: No; and there was no stone in the kidney.

Dr. Hanelin: The density observed may have been in the liver, then.

Dr. Ellis: Where did the bleeding come from?

Dr. Taft: I do not know. She had subserosal hemorrhages and hemorrhages under the endocardium and ecchymoses of the skin. I suspect that these were all the result of the low prothrombin time.

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SPEAKING OF CHRISTMAS

A CONSIDERATION of Christmas leads naturally to a consideration of books. The two, since the first became an occasion for giving and the second available for gifts, have become inseparable. Both, in their fundamental concept, are intended to appeal to man's more exalted emotions and to the nobler exercise of his intellect.

An argument in favor of good books and the reading of them as a therapeutic device was presented editorially in the *Saturday Review* in that dim period in man's progress now nearly six months past. At that time and in that periodical the reading of books was recommended as an antidote for "the excessive strain of modern living and the intense emotional pressures at work inside the individual." A book of verse, a loaf of bread and so forth, to say nothing of a jug of wine and thou, came immediately to the reader's mind.

Disraeli, plagiarizing an earlier authority, is reputed to have said that when in doubt he took to his bed. He must have known that nearly the same result can be achieved, without the trouble of undressing or even removing one's shoes, by taking to a book.

So much for books. The impelling thought is that modern (no less than ancient) man needs something that encourages contemplation — that removes him at more or less regular intervals from his concern with the obsessive realities of life. Physicians need not think that they alone are overwhelmed by progress; it simply happens that they, too, are gathered up in the same whirlwind that mankind in general has released to its own obfuscation.

The technical achievements of fifty years of progress have resulted in an increase in life expectancy — a noble achievement if a cheerful old age can also be achieved. They have contributed very little to those friendly relations that constitute one of the amenities of life; instead they have been responsible for the replacement of the corner grocer by the block-busting supermarket and for the production of a prosperity that, bringing little of spiritual value, has become a sort of spiritual liability. A century ago Wordsworth decided that the world was too much with us, and there has been little tendency over the years for its bleaker aspects to become more remote. A set of simple directional instructions that contribute to sustained and agreeable usefulness need to be remembered — "to think highly, to endure long and to love deeply." Only the second seems to have survived to any degree, and that perforce.

The diabolic payoff, to ensure that the physician's every waking moment shall be devoted to the pursuit of efficiency, is a recently announced tape-recorded medical lending library, the vocal element of which sits beside him in his car and pours into his ear, wherever he goes, precise abstracts of the world's most important medical literature. Nor is reversing the process a source of any relaxation; it simply enables him to dictate the products of his own cerebral activity, if any.

One is reminded of the worker on the assembly line whose efficiency was doubled by a wrench put in his left hand to turn up another nut while his right was similarly engaged. Pedals were then devised for him to operate with his feet, further to increase his output, while starry-eyed engineers bent over plans to put still other sets of his muscles into gainful employment.

LIBRARY REACHES FIRST OBJECTIVE

THE present leaders of the Boston Medical Library not only have proved to be devoted and inspiring directors of that venerable institution's affairs but also have demonstrated that such leadership can be turned into most productive channels.

It is well known that the Library, in extraordinarily active use despite the fact that it houses inadequately one of the country's great collections of medical literature, has had no addition to its physical facilities for over twenty years. The "new" wing was built in 1930, but owing to insufficient funds its elevator was never installed, the last six stack levels were never built and the periodical room, although in constant use since that time, was never finished — it is still a vault of painted brick walls and unfinished concrete ceiling.

FIGURE 1. *Unfinished Periodical Room.*

The Library's past president, Dr. Walter G. Phippen, made a great contribution to its welfare by assuring to it the support of the Massachusetts Medical Society. There has remained to his successor, Dr. Arthur W. Allen, the distinction of inaugurating and seeing through, largely by his own efforts and nearly to its conclusion, the initial phase of a campaign for funds that, when both phases are completed, will both furnish the Library with its needed physical facilities and provide an income sufficient for its continued service for many years to come.

The initial phase of the Greater Service Program had a minimum goal of $250,000, sufficient to put the building plan in motion, and a challenge goal of $300,000, which will not only bring to its completion the immediate building program but also take care of incidental costs. At the time of the last report the program stood within $31,000 of its challenge goal and had exceeded the minimum goal by nearly $20,000.

FIGURE 2. *Cavity to be Filled.*

This considerable sum, it is interesting to note, has been received from 1163 donors with an average gift of $294, including generous contributions from the Massachusetts Heart Association, the Massachusetts Division of the American Cancer Society and other scientific and clinical clubs and similar organizations. The friends and associates of the late Dr. Frank Howard Lahey have contributed an impressive sum to finish the periodical room as a memorial to that famous surgeon, and five additional memorial gifts have been made to commemorate other outstanding physicians.

Plans are already at hand for the installation of the elevator during the winter, and bids are being negotiated for the completion of the stack levels in the spring and summer of 1954.

The Boston Medical Library, as a result of these united efforts and the support that continues to make itself felt, is going definitely over the top. Nothing succeeds, apparently, like success!

ANTIBIOTIC SYMPOSIUM

Some provocative opinions were expressed during the Antibiotic Symposium held in Washington, D. C., October 28 to 30, under the chairmanship of Dr. Henry Welch and sponsored by the Division of Antibiotics, Food and Drug Administration of the Department of Health, Education and Welfare in collaboration with the journal, *Antibiotics and Chemotherapy*. In addition to a few general addresses by a small group of invited speakers and discussers, nearly 100 papers were presented. These dealt largely with various new aspects of antibiotics that are already available commercially, some data being presented about a few that are not yet available. The majority of participants were workers from the research and development laboratories of the various manufacturers, but many were from medical schools, hospitals and other research laboratories. The general papers and discussions summarized the present status of various aspects of antibiotic treatment, including a general survey of the clinical uses of the agents presently available; the effects of the emergence of resistant strains on the future of antibiotic therapy; the importance of hypersensitivity reactions; the combined action of antibiotics; and the present status of the treatment of tuberculosis and syphilis and of the use of antibiotics in surgical infections.

As a result of the excessive and unnecessary prescription of antibiotics by the medical profession large and ever-increasing numbers of persons are being sensitized to them, making it difficult, and sometimes even dangerous, to administer these valuable agents when they may be specifically indicated and might even be life saving. Moreover, increasing numbers of strains of certain organisms, notably the staphylococci, are becoming appreciably resistant to the antibiotics most widely used.

On the other hand, serious or even fatal reactions, though they are reported from time to time, are really extremely infrequent when considered in relation to the vast numbers of patients to whom the drugs are given. This risk is further reduced when one takes into account the thousands of lives that are undoubtedly saved as the result of their use. Antimicrobial resistance to antibiotics may also be important in staphylococcal infections or during prolonged management of chronic tuberculosis, and perhaps in some other infections like those due to proteus and pseudomonas, which have not, at any time, been successfully treated. The phenomenon has not been encountered in infections against which the antimicrobial agents have been most highly effective and for which they have been most successfully employed — notably, gonorrhea, meningococcal meningitis, infections due to the hemolytic streptococcus, syphilis, pneumonia, rickettsial diseases and others.

One of the more significant of the new developments described at this symposium concerned the preparation, laboratory testing and preliminary clinical trial of a new antibiotic, tetracycline. The structure of tetracycline is common to both chlortetracycline and oxytetracycline; it lacks both the organic chlorine atom that characterizes the former and the OH group that distinguishes the latter. Tetracycline was prepared from chlortetracycline by catalytic hydrogenation in the presence of palladium. This was accomplished by research workers of both the Lederle Laboratories and Charles Pfizer and Company. Studies were also presented by personnel of the Antibiotic Research Division of Heyden Chemical Company, who reported that they had obtained tetracycline by direct fermentation with the use of an organism originally isolated from a sample of soil from Texas.

All the groups who reported on studies concerning tetracycline appeared to agree that it has the same activity in vitro and in experimental infections as the previously available analogues, chlortetracycline and oxytetracycline. Tetracycline, however, appears to be more stable and may have some other favorable pharmacologic properties, one of which is that it can be demonstrated in the cerebrospinal fluid of normal human beings and in laboratory animals.

Only a few clinical reports on the use of tetracycline were presented, the largest number of patients having been treated at the Boston City Hospital. The results of these initial clinical trials indicated that tetracycline probably has the same therapeutic effect as chlortetracycline and oxytetracycline but is much less toxic; the untoward gastrointestinal symptoms in particular were apparently much less frequent with tetracycline than with either of the antecedent analogues.

A new repository preparation of penicillin, dibenzylamine penicillin G, was described, and more data concerning dibenzylethylenediamine (DBED) dipenicillin G* were also presented. The former seems to have a prolonged action intermediate between that of the latter and that of procaine penicillin. Among the other new antibiotics discussed, some were found to have special and highly specific activities, but none seemed destined to be used widely in the near future or to compete with the agents already available commercially.

Among the reports dealing with the presently available antibiotics, one of special significance concerned epidemiology of erythromycin-resistant staphylococci in a hospital population. In the hospital where this study was carried out, all strains of staphylococci isolated at the beginning of the study and before the use of erythromycin was begun were highly sensitive to that antibiotic. After five months 75 per cent of the strains of staphylococci isolated from the hospital personnel were almost totally resistant. During the same time, the incidence of erythromycin-resistant staphylococci isolated from the tracheas of patients who were tracheotomized increased from 0 to 95 per cent in a three-month period. As the organisms increased in resistance, erythromycin became progressively less effective in preventing or eradicating staphylococcal infections.

In this connection, one practical application of the use of antibiotic combinations was reported. The combination of erythromycin with either streptomycin or bacitracin proved successful in a small number of cases of bacterial endocarditis, apparently preventing the development of erythromycin resistance in the infecting organisms that was the troubling feature of previous attempts to treat such infections with erythromycin alone.

All the papers and the discussions are to be published as a separate volume under the editorship of Dr. Henry Welch to accompany the December issue of *Antibiotics and Chemotherapy*. This volume should prove useful to all interested in this important field.

*Also known under the Wyeth trade-mark "Bicillin."

BRITAIN'S HEALTH SERVICE

Miss Patricia Hornsby-Smith, member of Parliament and Parliamentary under-secretary to the British Ministry of Health, who proved such a gracious official Government hostess to the First World Conference on Medical Education in London last August, interpreted Britain's National Health Service at a recent Harvard School of Public Health Forum.

Miss Hornsby-Smith dealt especially with certain misapprehensions regarding the Health Service that are current on this side of the water, where most of the medical profession and a majority of the voters are fearful lest a similar system be introduced. Two misapprehensions in particular were Miss Hornsby-Smith's concern: that the program "is wholly the child of the Socialist Party," and that it is an insurance scheme.

As is not too clearly understood in America, the present Service, Miss Hornsby-Smith stressed, was developed by a Conservative minister in the wartime Coalition Government, and was put into effect by the Labor Government. It fills a critical British need and is accepted by a majority in Britain and by all parties as essential to British well-being. It is not a form of insurance, as are cash benefits for unemployment, retirement, industrial injury, maternity and death, but is a direct tax-supported service.

Under national health insurance, instituted in 1911, some 20,000,000 Britons paid insurance and were entitled to medical attention without further charge; under the National Health Service every member of the population is eligible for free medical, surgical and hospital care. The British, according to Miss Hornsby-Smith, do not like the term "socialized medicine," although, accepting as a definition of socialism "a policy or practice" based on the theory of "collective or governmental ownership and democratic management of the essential means for the production and distribution of goods," it is hard to see how the implication can be avoided, if service is substituted for goods. By the same token a system of socialized education, at state and municipal levels, is operative in this country.

What is necessary or desirable for the British, many of whom, through many hard years, have had little or no medical attention, is not necessarily desirable in America, where the distribution of medical care has been less limited and where voluntary methods of prepayment are relatively more effective. A way of dealing with a problem as it exists in Great Britain should not be criticized simply because it would not be applicable to this country.

Transactions of the American Medical Association. — *We understand that the efforts made by the Publishing Committee and the gentlemen named in the Journal of No. 23d, together with the low price of the volume there mentioned, have greatly increased its circulation.*

Boston M. & S. J., *December 21, 1853.*

BOSTON MEDICAL LIBRARY

HISTORY OF PERUVIAN MEDICINE

The early history of Peru and of its inhabitants is unknown; its modern history begins with the Incas, probably in the thirteenth century. The country was conquered by Spain early in the sixteenth century, and after a period of internal strife, it achieved independence in 1825, when it became a republic.

Dr. Juan B. Lastres* has written the history of Peruvian medicine from prehistoric to modern times in 3 large volumes, dealing with the periods of the Incas, the Viceroyalty and the Republic. The text is profusely illustrated with reproductions of documents, important books, personages and physicians, and historical objects. The history is an outstanding accomplishment in its field.

*Lastres, J. B. *Historia de la Medicina Peruana.* 3 vol. 1107 pp. Lima: Universidad Nacional Mayor de San Marcos, 1951. (Vol. 5 of the *Historia de la Universidad Nacional.*)

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Rose and Carless' Manual of Surgery, for Students and Practitioners. By Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., fellow of King's College, London, president of the Royal College of Surgeons of England, senior surgeon, King's College Hospital, director of surgical studies and lecturer in surgery, King's College Hospital Medical School, surgeon, Belgrave Hospital for Children and Royal Masonic Hospital, consulting surgeon to the Royal Navy, and examiner in surgery to the University of Cambridge. Assisted by 18 contributors. Eighteenth edition. 8°, cloth, 1471 pp., with 1011 illustrations. Baltimore: Williams and Wilkins, 1952. $12.00.

This British book has had an unusual printing history. First published in 1898, it has gone through 46 printings in England and America, and has been translated into Arabic, Chinese (3 editions) and Hungarian; the editor, Sir Cecil Wakeley, is an eminent British surgeon. It is the joint work of 18 specialists in their peculiar fields. It is a practical book and does not refer to any literature. There is a good index. The printing, which was done in Great Britain, is excellent.

NOTICES

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the Cheever Amphitheater, Boston City Hospital, on Wednesday, January 13, 1954, at 8 p.m. There will be a symposium on "Gastrointestinal Bleeding" conducted by Drs. Thomas Warthin and J. Englebert Dunphy.

LABORATORY DIAGNOSIS OF VIRUS DISEASES

A course in the laboratory diagnosis of virus diseases will be presented by the Laboratory Branch, Communicable Disease Center, at the Virus and Rickettsia Section Laboratory in Montgomery, Alabama, March 15 through 26, 1954. Information and application forms may be obtained from Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, Box 185, Chamblee, Georgia.

COLLEGE OF MEDICAL EVANGELISTS ALUMNI POSTGRADUATE CONVENTION

The Alumni Association of the College of Medical Evangelists will sponsor a two-day refresher course, intended primarily for general practitioners, before the three-day convention to be held at the Biltmore Hotel, Los Angeles, February 23 to 25, 1954. The registration is open to all physicians. Requests for information should be sent to the Managing Director, Walter B. Crawford, 316 North Bailey Street, Los Angeles 33, California.

AMERICAN FEDERATION FOR CLINICAL RESEARCH

The annual meeting of the Eastern Section of the American Federation for Clinical Research will be held in the Jimmy Fund Building, Children's Medical Center, Boston, on January 4, 1954, at 9 a.m. The officers of the Eastern Section are Drs. Joseph R. Stanton, Chairman, Walter E. Judson, Program Committee Chairman, and Walter L. Goodale, Arrangements Committee Chairman.

AMERICAN PSYCHOSOMATIC SOCIETY

The eleventh annual meeting of the American Psychosomatic Society will be held at the Jung Hotel, New Orleans, March 27 and 28, 1954. There will be a panel on neoplastic disease and neurophysiologic mechanisms. There will be a registration fee for nonmembers. Further information may be obtained from Dr. George L. Engel, President, American Psychosomatic Society, 551 Madison Avenue, New York 22, New York.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 28. American Association for the Advancement of Science. Page 828, issue of November 12.

DECEMBER 28–30. American Society of Human Genetics. Page 914, issue of November 26.

JANUARY 4. New England Cardiovascular Society. Page 1004, issue of December 10.

JANUARY 4. American Federation for Clinical Research, Eastern Sectional Meeting. Notice above.

JANUARY 6, MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

JANUARY 13. Boston Gastroenterological Society. Notice above.

JANUARY 22, 23, 29 and 30. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JANUARY 26. Massachusetts Hospital Association. Hotel Statler, Boston.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 5 and APRIL 9. New England Society of Anesthesiologists. Page 914, issue of November 26.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

FEBRUARY 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Notice above.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Notice above.

MARCH 27 and 28. American Psychosomatic Society. Notice above.

MAY 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

(*Notices concluded on page xx*)